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Éditorial

Les établissements scolaires, des lieux essentiels lors des campagnes de vaccination contre le méningocoque

Schools, essential places during vaccination campaigns against meningitis

Mots clés : Vaccination ; École ; Enfants ; Méningocoque

Keywords: Vaccination; School; Children; Meningitis

Les infections à méningocoques font parties des principales causes de décès chez les jeunes enfants et restent une cause important de morbidité et de mortalité dans le monde. La clé essentielle pour réduire l'incidence de ces infections reste et demeure la prévention par la vaccination car les premiers signes de la maladie peuvent être non distincts et l'infection peut évoluer rapidement jusqu'à devenir mortelle dans 5 à 10 % des cas, même en cas de traitement initié dès le début [1].

Malgré tout, il faut souligner qu'en France à peine plus d'un quart des adolescents est vacciné contre le méningocoque C, compromettant ainsi l'effet de cette vaccination [2]. Alors que l'utilisation d'un vaccin adapté fournit une protection directe et a notamment permis de réduire le nombre de méningites à méningocoque C de 87 % entre 2001 et 2012 [3]. L'utilisation d'un vaccin contre les méningocoques apparaît donc efficace pour réduire l'incidence de la pathologie dans le cadre de campagnes de vaccination.

L'information envers les populations est le point clé dans toute campagne de vaccination. D'ailleurs, par exemple, la principale raison citée par les parents d'acceptation de la vaccination contre le méningocoque B avec le vaccin Bexsero® reste la protection contre la méningite [4]. Ce désir de protection est aussi soulevé par les adolescents. À l'inverse, la raison la plus fréquente mentionnée par les parents qui n'entendent pas faire vacciner leur enfant est l'opposition à la vaccination en général. Pour les adolescents, le manque d'intérêt, de temps ou d'informations sont principalement évoqués comme arguments contre cette vaccination [5,6].

Toutefois, de nombreuses études ont montré que les nouveaux vaccins sont susceptibles d'engendrer des doutes et des inquiétudes [4,7]. Elles font ressortir que la moitié des parents craignent que les nouveaux vaccins ne soient pas aussi sûrs que les anciens vaccins ou encore que les enfants reçoivent toujours trop de vaccins [4]. Toutefois, dans des contextes particuliers de situation endémiques, la menace de la maladie peut l'emporter sur les risques perçus liés aux nouveaux vaccins.

Une couverture médiatique avant le lancement d'une campagne de vaccination peut ainsi participer à l'augmentation de la perception du risque en cas de non-vaccination au regard de la dangerosité de la maladie. Cette perception est d'autant plus importante que la méningite est une maladie très grave et que de nombreuses études reflètent les hauts niveaux d'acceptabilité du vaccin [4,8]. La maladie peut survenir de façon imprévisible, les symptômes se développer rapidement et entraîner de graves conséquences. Toutes ces caractéristiques font augmenter la perception du risque au sein de la population.

Il est donc important d'adapter la communication à la population cible en tenant compte de ses disparités. Ainsi, dans le cadre d'une campagne de vaccination contre le méningocoque, il semble pertinent d'axer spécifiquement la communication vers les adolescents car ils apparaissent comme moins préoccupés par leur propre risque de contracter la méningite en cas d'endémie que le reste de la population [5].

De même, implanter directement les centres de vaccination au sein des établissements scolaires a pour énorme avantage de se rapprocher au plus près de la population cible des enfants/adolescents à vacciner. Ces actions d'aller vacciner directement au sein des écoles sont d'ailleurs reconnues comme un moyen d'augmenter la couverture vaccinale des adolescents [9].

Il est important que dès le début de la campagne de vaccination les chefs d'établissements scolaires soient associés aux réunions d'information et des phases d'écriture de la planification des campagnes de vaccination ayant lieu dans leurs

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établissements [10]. Leur implication forte peut permettre de faire adhérer de façon plus efficace l'ensemble du personnel éducatif et de santé scolaire à la nécessité de faire vacciner les enfants et adolescents et ainsi éviter de futures résistances contre la vaccination pour de prochaines planifications d'interventions [11]. Leur rôle est donc central et leur implication essentielle dans la bonne réalisation de campagnes de vaccination en établissements scolaires.

Actuellement, la France dispose d'une offre de vaccination importante mais essentiellement disponible dans des centres spécifiques présents dans les centres-villes. Ceux-ci peuvent apparaître comme difficilement accessibles pour les populations qui en sont éloignées géographiquement, les familles ou encore celles qui ne les connaissent pas [12]. Développer des équipes mobiles, se déplaçant dans l'ensemble des établissements scolaires des zones concernées par les campagnes de vaccination contre le méningocoque, peut apparaître comme une solution efficace comme moyen de prévention et de communication afin d'élargir le taux de couverture vaccinal en s'approchant au plus près des populations cibles.

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General review

Multidrug and extensively drug-resistant tuberculosis

Tuberculoses à bacilles multi- et ultrarésistants

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Abstract

The emergence of drug-resistant tuberculosis (TB) compromises global tuberculosis control. The incidence of multidrug-resistant strains (MDR) defined as resistant to the two main antituberculosis drugs, rifampicin and isoniazid, was raised in the 1990s. Ten percent of these strains have developed additional resistance to the main second-line antituberculosis drugs: fluoroquinolones and aminoglycosides. These strains are defined as extensively drug-resistant (XDR). The prognosis of MDR-TB and XDR-TB is poor due to limited therapeutic resources. However, many new innovations may lead to a radical change in this field. Genotypic testing is now able to detect drug resistance within a few hours. Genotypic diagnosis of rifampicin resistance is now recommended in France for each new case of TB. The currently recommended treatment for MDR-TB is long (18–24 months) and toxic. It is, however, on the verge of being replaced by a 9-month treatment. New antituberculosis drugs such as bedaquiline and delamanid should also improve the prognosis of MDR-TB and XDR-TB.

Keywords: Tuberculosis; Multidrug resistance; Extensively drug resistance; Delamanid; Bedaquiline

Résumé

L'émergence des tuberculoses (TB) à bacilles résistants aux antituberculeux compromet le contrôle mondial de la tuberculose. Les souches multirésistantes (MDR), c'est-à-dire résistantes à l'isoniazide et à la rifampicine, sont apparues dans les années 90. Parmi ces souches, 10 % ont développé des mécanismes de résistance supplémentaires aux principaux antituberculeux de deuxième ligne : les fluoroquinolones et les aminosides. Ces souches sont dites ultrarésistantes (XDR). Le pronostic de ces tuberculoses est sombre compte tenu du peu de ressources thérapeutiques disponibles. Toutefois, de nombreuses nouveautés permettent d'envisager un changement radical dans la prise en charge de ces cas. Sur le plan diagnostique, les tests génotypiques permettent de faire un diagnostic des résistances aux antituberculeux en quelques heures. Il est désormais recommandé de réaliser un diagnostic génotypique de résistance à la rifampicine pour tout nouveau cas de tuberculose. Sur le plan thérapeutique, le traitement de référence actuel pour les cas MDR, qui est long (18 à 24 mois) et toxique, est en passe d'être remplacé par un traitement court de 9 mois. Enfin, de nouveaux antituberculeux comme la bédaquiline et le delamanid offrent des perspectives d'amélioration du traitement des tuberculoses MDR et XDR.

Mots clés : Tuberculose ; Multirésistance ; Ultrarésistance ; Bédaquiline ; Delamanid

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1. Introduction

Tuberculosis (TB) is still a major public health problem and remains a leading cause of death worldwide, particularly in developing countries. The incidence of TB is considerably lower than what it used to be in industrialized countries, but the fight against TB is now confronted to a new problem: the emergence of resistance to antituberculosis drugs.

2. Background and definitions

Streptomycin was first used in the treatment of pulmonary TB in 1948. Relapses were however already being reported following a temporary improvement in patients presenting with infections caused by strains that had become resistant to the antibiotic [1]. A combination of antibiotics is theoretically supposed to prevent the selection of resistant mutants. However, antibiotic misuse led to the emergence of strains resistant to the main antituberculosis drugs. TB cases resistant to the two main antituberculosis drugs, isoniazid and rifampicin, were observed as early as the 1990s [2]. These strains are defined as multidrug-resistant (MDR). The main antituberculosis drugs used in the treatment of MDR-TB are fluoroquinolones and last-line injectable drugs (amikacin, kanamycin and capreomycin). Their use led to the selection of MDR strains that developed additional resistance mechanisms to fluoroquinolones and aminoglycosides [3]. These strains are known as extensively drug-resistant (XDR). The term "pre-XDR" is sometimes used to define fluoroquinolone-resistant or last-line injectable drug-resistant MDR-TB.

3. Resistance mechanism to antituberculosis drugs

Mycobacterium tuberculosis infection is characterized by the multiplication of bacilli, up to 10^8 bacilli in cavities. Just like any other bacterium, *M. tuberculosis* acquires mutations during genome replication. Some of these mutations lead to the development of resistance to antituberculosis drugs. The incidence of those mutations is quite low: 10^{-5} for isoniazid and 10^{-7} for rifampicin. A tuberculous cavity with 10^8 bacilli contains 1,000 isoniazid-resistant bacilli and 10 rifampicin-resistant bacilli. These resistant mutants are progressively selected in case of isoniazid-based or rifampicin-based monotherapy.

The World Health Organization (WHO) has thus been recommending since the 1960s the use of a combined treatment, with at least three antibiotics, to avoid the emergence of resistant mutants. As mutations are independent from one another, resistance mutations to isoniazid and rifampicin will unlikely occur in the same bacterium ($10^{-5} \times 10^{-7} = 10^{-12}$), and the few strains resistant to both of these antibiotics will be eradicated by the remaining molecule included in the combination. However, the results of a modeling study of the emergence of resistance indicate a higher frequency of multidrug-resistant strains (10^{-4}) [4]. The wide variety of tuberculosis lesions may also lead to a monotherapy effect in one lesion while the prescribed treatment is a combination therapy [5]. A poorly implemented and managed antituberculosis treatment may act as a monotherapy on some strains and thus lead to the selection of resistant mutants. This is called an acquired or secondary resistance. When these resistant strains are transmitted to close contacts, newly infected patients contract a form of TB that is already resistant to antituberculosis drugs. This is known as primary resistance. These patients will receive treatment and might acquire new resistance (Fig. 1). This is how a susceptible strain may become an XDR strain. This process has been described over a 10-year period in South Africa [6].

Table 1
The 27 countries with the highest proportion of MDR-TB case patients in 2014 according to WHO [7].
Les 27 pays à plus forte proportion de tuberculoses à bacilles MDR en 2014 d'après l'OMS [7].

Countries	% of MDR-TB among	
	Newly diagnosed patients	Treated patients
Belarus	34	69
Kyrgyzstan	26	55
Kazakhstan	26	58
Moldova	24	62
Uzbekistan	23	62
Ukraine	22	55
Russia	19	49
Estonia	19	62
Lithuania	14	49
Azerbaijan	13	28
Georgia	12	39
Armenia	9.4	43
Latvia	8.2	30
Tajikistan	8	52
China	5.7	26
Myanmar	5	27
Vietnam	4	23
Pakistan	3.7	18
Nigeria	2.9	14
Bulgaria	2.3	23
Democratic Republic of Congo	2.2	11
India	2.2	15
Philippines	2.0	21
Indonesia	1.9	12
South Africa	1.8	6.7
Bangladesh	1.4	29
Ethiopia	1.6	12

4. Epidemiology of MDR-TB and XDR-TB

The last WHO report indicates that approximately 480,000 new MDR-TB case patients were reported worldwide in 2014, of which 10% were XDR-TB [7]. Most of these newly reported resistant and susceptible TB case patients were observed in South East Asia, Sub-Saharan Africa and Eastern Europe. China, India, and Russia report 54% of global MDR-TB case patients. This is mainly due to their large population. Measuring the proportion of MDR-TB case patients in relation to all TB case patients reported in a specific country is the most effective way to assess the individual risk of multidrug resistance. The last WHO report details a list of 27 countries with a high proportion of MDR-TB case patients (Table 1). Most of these case

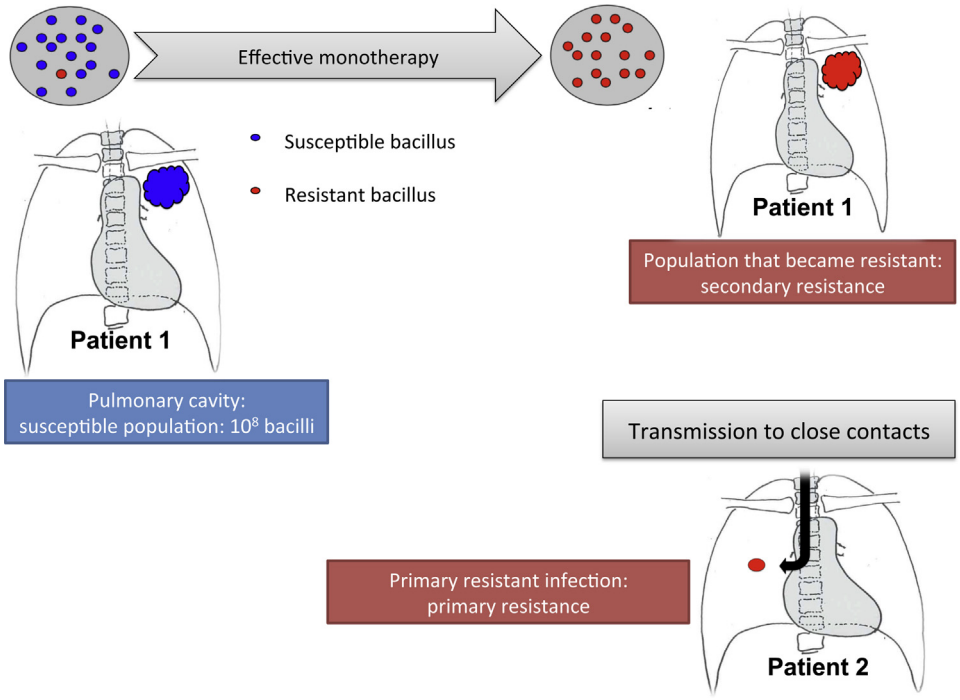

Fig. 1. Selection mechanisms of antituberculosis drug resistance in *M. tuberculosis*.
Mécanisme de sélection des résistances aux antituberculeux chez M. tuberculosis.

patients were reported in Eastern Europe countries. A newly infected patient incurs for instance a 12%, 22%, and 19% risk of being infected by a MDR strain in Georgia, Ukraine, and Russia, respectively [7].

The incidence of MDR-TB in France used to stagnate around 1% of all TB case patients from 2002 to 2010. It has now doubled since 2012 with approximately 100 newly reported case patients per year [8]. XDR strains also emerged at the same time and now account for 25% of MDR-TB case patients in France [9]. These epidemiological changes, specific to France since 2012, are due to the arrival of patients coming from countries of the former Soviet Union, and mostly from Georgia [10]. Half of the new cases of MDR-TB are located in the Île-de-France department. These patients are usually young, with a median age of 32 years. More than half of patients from Eastern Europe countries have already received an antituberculosis treatment.

5. Prognosis of MDR-TB and XDR-TB

The therapeutic resources available to treat MDR-TB and XDR-TB patients are very limited, hence the poor prognosis. The one-year mortality is estimated at 10% for susceptible TB patients, but increases to 17% and 23% for patients infected by MDR and XDR strains, respectively [11]. Fluoroquinolones are the most effective second-line antituberculosis drugs in the treatment of MDR-TB [12]. The emergence of fluoroquinolone resistance greatly impacts the poor prognosis of XDR-TB [13].

The prognosis of MDR-TB improved over the past few years thanks to (i) the creation of specialized teams [14], (ii) the implementation of customized treatment protocols [14], and (iii) the launch of new antibiotics active against *M. tuberculosis* such as linezolid [15] and bedaquiline [16,17].

The retrospective analysis of French MDR-TB case patients managed in 1994 indicates, for instance, that the rate of treatment success at two years was 41.5% [18]. In light of this alarming evidence, the French reference center for mycobacteria and mycobacteria resistance to antituberculosis drugs (French acronym CNR-MyRMA) developed a new program including a quicker reporting of suspected case patients, a comprehensive antimicrobial susceptibility testing for each MDR strain using conventional and molecular techniques, and the implementation of multidisciplinary meetings with experts from various specialties (microbiologists, pulmonologists, infectious disease specialists, pediatricians, pharmacology specialists). This new management led to an increased rate of treatment success at three years: 70% for the cohort of patients diagnosed in 1998 and 1999 [19]. The prognosis of patients presenting with XDR-TB is far less optimistic, with mortality rates reaching 50% to 100% [20–23]. Therapeutic success is however always related to the number of effective antibiotics still available to treat patients [14]. High hopes are invested in antituberculosis drugs in development because of the very limited number of effective molecules for patients presenting with XDR-TB.

6. Diagnosis of MDR-TB and XDR-TB

In France, 90% of rifampicin-resistant strains are also resistant to isoniazid in HIV-negative patients. Detecting rifampicin resistance is thus predictive of a multidrug-resistant strain. The resistance status diagnosis may be established by phenotypic or genotypic tests.

The proportion method is the reference method for phenotypic testing [24]. The proportion of resistant mutants to a given antibiotic within a population of bacilli is determined at a given antibiotic concentration (critical concentration). The strain is considered resistant to the antibiotic if the proportion is superior to the proportion of resistant mutants of a wild strain (critical proportion). These tests take time as bacilli must be put into culture for up to 3–8 weeks because of the long doubling time of *M. tuberculosis* (20 hours). Genotypic assays have been developed to compensate for the long time required for phenotypic testing.

Rifampicin targets the RNA polymerase encoded by the *rpoB* gene. Rifampicin resistance is almost always caused by a mutation occurring in the *rpoB* gene. Mutations may be detected by sequencing the *rpoB* gene or using commercial molecular assays (Xpert®MTB/RIF, GenoType MTBDRplus®, INNOLIPA Rif-TB®). These techniques will look for the presence of the most frequently observed mutations among rifampicin-resistant strains. These molecular assays allow for a quick resistance diagnosis, within a few hours only. Every positive result obtained at microscopic examination or every culture yielding *M. tuberculosis* must be further investigated with a rifampicin mutation detection test performed within 72 hours. When a mutation conferring rifampicin resistance is detected, it is advised to confirm the result using another technique and, if possible, another sample [25]. Some of the available assays help detect mutations associated with isoniazid resistance (GenoType MTBDRplus®) or with resistance to the second-line antituberculosis drugs (GenoType MTBDRsl®). The hierarchized use of these tests, just like in the algorithm used by the CNR-MyRMA in France, helps reduce the time to diagnosis of antituberculosis drug resistance (Fig. 2).

These tests are associated with an excellent efficacy in detecting resistance to rifampicin (*rpoB* gene) [25–27], with a good efficacy for isoniazid (*inhA* and *katG* genes) [28,29], fluoroquinolone (*gyrA* gene), amikacin, and capreomycin resistance (*rrs* gene) [29]. They are, however, far from being optimal to detect kanamycin (*rrs* gene) and ethambutol resistance (*embB* gene) [30]. The first-line antituberculosis treatment should be based on the results of the genotypic test, and should then be adapted to the results of the phenotypic test (Fig. 2).

7. Managing MDR-TB and XDR-TB patients

7.1. Preventing the emergence of resistance to antituberculosis drugs

7.1.1. Preventing secondary resistance

Improving the management of patients presenting with TB caused by susceptible strains and by strains only resistant to isoniazid is one of the most important step in the fight against the emergence of MDR-TB and XDR-TB. The conventional treatment of TB caused by susceptible strains is a combination treatment with rifampicin and isoniazid prescribed for the whole treatment duration (six months), and pyrazinamide and ethambutol for the first two months of treatment. Ethambutol is a second-rate antituberculosis drug; it is only used to avoid prescribing rifampicin monotherapy in case of isoniazid resistance in lesions unresponsive to pyrazinamide. Susceptibility to isoniazid must therefore be confirmed before prescribing the maintenance treatment with rifampicin and isoniazid so as to avoid the emergence of MDR-TB. There is currently no consensus on the treatment of TB caused by strains only resistant to isoniazid. The most recent French recommendations advise to keep on prescribing ethambutol for the whole duration of treatment [25].

The use of fluoroquinolones should be discussed with regard to the risk of selection of resistant strains to these key antibiotics for the treatment of MDR-TB.

7.1.2. Preventing primary resistance

Sputum-smear positive MDR-TB must quickly be diagnosed to implement airborne precautions and avoid any secondary case patients. The microscopic examination of respiratory samples and molecular tests for detecting resistance to rifampicin help diagnose these patients within a few hours [25].

Patients at high risk of TB must be placed in solitary confinement before receiving the microbiological test results. A history of antituberculosis treatment is the main risk factor for multidrug resistance, even more so with a recent treatment [8]. Coming from specific geographical areas, particularly from the former Soviet Union countries, is also considered a risk factor (Table 1). The recent disease epidemiology in France is characterized by the high proportion of patients coming from Eastern Europe (2/3 of case patients). One third of these patients come from Georgia [10]. Isolation precautions must be taken at admission for any patient suspected of having TB, especially if the patient presents with risk factors for antituberculosis drug resistance. Patients presenting with high-inoculum TB, such as pulmonary cavity presentations, are 3.5 times more likely to contract XDR-TB [31].

7.2. Treatment of MDR-TB and XDR-TB

7.2.1. Therapeutic treatment

A poorly implemented or managed treatment will lead to treatment failure, and may lead to the selection of additional resistance. For patients at high risk of resistance, it is advised to wait for the results of the genotypic testing of rifampicin resistance before initiating the standard treatment. When the MDR nature of the infection is confirmed, the results of the genotypic tests help guide the initial treatment while those of the phenotypic tests are used to adapt the previously initiated treatment (Fig. 2). MDR-TB and XDR-TB treatment must be implemented on a case-by-case basis and must be discussed among experts [7,14,32,33] such as those attending the monthly multidisciplinary meetings organized by the CNR-MyRMA in France.

Treatment is implemented according to WHO recommendations [7,33]. It must include four or five antituberculosis drugs, to which the strain is susceptible, to limit the risk of selecting new resistance.

There are currently six groups of antituberculosis drugs (Table 2). They are grouped together on the basis of their

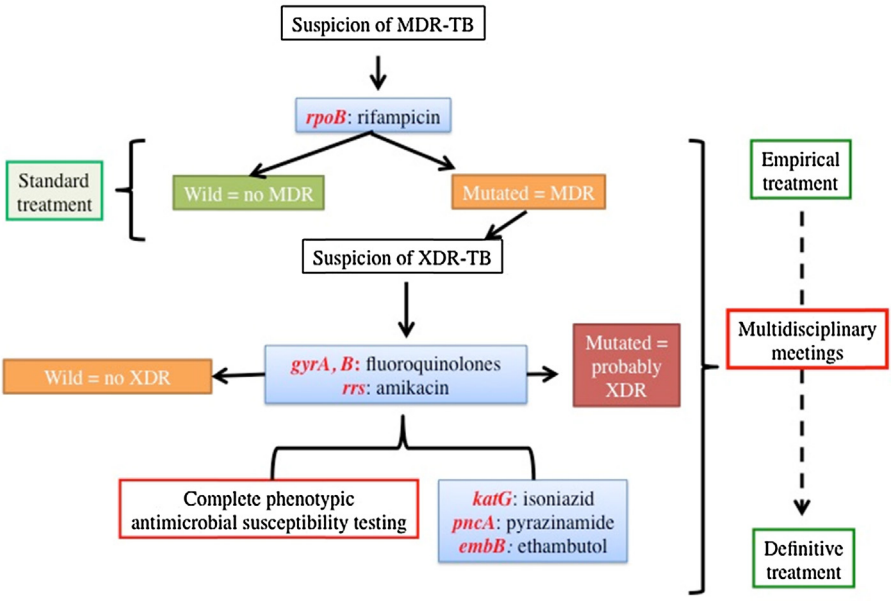

Fig. 2. Diagnostic algorithm of antituberculosis drug resistance used by the CNR-MyRMA in France.
Algorithme diagnostique de la résistance aux antituberculeux appliqué par le CNR-MyRMA en France.

Table 2
Antituberculosis drug classification according to WHO [33].
Classification des antituberculeux d'après l'OMS [33].

Groups of antituberculosis drugs	Molecules
A: fluoroquinolones	Levofloxacin
	Moxifloxacin
	Gatifloxacin
B: second-line injectable agents	Streptomycin
	Kanamycin
	Amikacin
	Capreomycin
C: other core second-line agents	Ethionamide/prothionamide
	Cycloserine/terizidone
	Linezolid
	Clofazimine
D: add-on agents (not part of the core MDR-TB regimen)	D-1
	Pyrazinamide
	Ethambutol
	high-Dose isoniazid
	D-2
	Bedaquiline
	Delamanid
	D-3
	p-aminosalicylic acid
	Imipenem–cilastatin
	Meropenem
	Amoxicillin–clavulanic acid
	Thioacetazone

activity against *M. tuberculosis*, their cost and their tolerability. This classification was recently updated putting the use of new antituberculosis drugs such as delamanid, linezolid and bedaquiline forward [16,33].

The use of fluoroquinolones (moxifloxacin, gatifloxacin, and high-dose levofloxacin) should be favored as they are the most effective molecules among second-line drugs (group A) [34]. With regard to aminoglycosides (group B), the use of streptomycin is avoided because of the high frequency of primary resistance to this antibiotic (without any cross-resistance with other aminoglycosides). In case of fluoroquinolone prescription, the aminoglycoside may be discontinued three months after culture negativity. However, if a fluoroquinolone cannot be prescribed, the risk of treatment failure is higher and the aminoglycoside treatment must be prolonged for six months or one year after culture negativity.

The group C clusters other core second-line agents with old oral bacteriostatic molecules such as ethionamide and cycloserine, and new molecules such as oxazolidinones and clofazimine. Oxazolidinones are inhibitors of the bacterial ribosome. Linezolid is currently the only molecule available. Its *in vitro* activity against *M. tuberculosis* has been well-known for the past 20 years [35]. A phase II clinical study showed that linezolid contributed to decrease the time to negative culture when associated with treatments prescribed for XDR-TB. However, its long-term toxicity (myelosuppression, optic neuritis, peripheral neuropathy) greatly limits its use [36]. Clofazimine was initially developed as a treatment for leprosy in the 1950s. The molecule is now very useful because of the emergence of resistant TB strains. Its efficacy was recently assessed in a randomized study of 105 patients presenting with MDR-TB [37]. Adding clofazimine to the antituberculosis treatment is believed to reduce the time to culture negativity and to cavity closure.

The add-on agents (group D) include drugs which do not form part of the core second-line agents. Some new antituberculosis drugs of this group have a strong activity (group D-2) while other molecules – older ones – are not very effective (group D-3). As part of the group D-2, bedaquiline and delamanid are promising new antituberculosis drugs used in the treatment of XDR-TB and MDR-TB in the absence of other therapeutic options. Bedaquiline is an inhibitor of the mycobacterial ATP synthase [38]. As its mechanism is very specific,

there is no cross-resistance with other antituberculosis drugs [37,38]. Bedaquiline is therefore very effective against MDR or XDR strains [39]. It also has an *in vitro* activity against dormant bacilli [40]. This satisfactory sterilizing activity makes bedaquiline potentially useful to reduce treatment duration. Its bactericidal activity is stronger than that of isoniazid at similar doses [38]. Combining bedaquiline and pyrazinamide (group D-1) induced a synergistic efficacy in animal and human models [41,42]. The most impressive result was observed in a randomized study of patients infected by multidrug-resistant strains. This study aimed to compare the standard treatment of MDR-TB with that same treatment associated with bedaquiline or a placebo. After two months, the proportion of patients with negative sputum smear cultures was 48% in the placebo group and 9% in the bedaquiline group [16]. The benefit observed in the bedaquiline group was sustained for six months, even though bedaquiline was discontinued at the end of the second month of treatment [43]. An excessive mortality rate was however observed in the bedaquiline group compared with the placebo group. This excessive mortality was however not confirmed later on [17,44], but it should lead physicians to use the molecule with caution considering the associated QT prolongation. Delamanid has the same mechanism of action as PA-824 [44]. Its bactericidal activity was higher than that of the standard four-drug combination therapy when associated with rifampicin and pyrazinamide in a mouth model [44]. When administered in humans and compared with placebo, delamanid increases the recovery rate of patients presenting with MDR-TB [45]. Bedaquiline and delamanid are both very promising in the treatment of TB. They both have a temporary marketing authorization in France in the treatment of XDR-TB and MDR-TB in the absence of other therapeutic options. These molecules should help reduce treatment duration of resistant TB.

WHO recommends a MDR-TB regimen composed of at least five drugs including four core second-line drugs (one from groups A and B and two from group C) plus pyrazinamide. If a minimum of four core second-line drugs cannot be reached, drugs from groups D-2 or D-3 are added [33].

7.2.2. Treatment duration

WHO recommends an 18- to 24-month treatment duration based on the severity and number of lesions, tolerability, and efficacy of the prescribed antituberculosis drugs. The satisfactory sterilizing activity of some antituberculosis drugs – especially the new ones [46,47] – should lead to reduced treatment duration for MDR-TB. A shorter treatment would limit the associated toxicity, increase treatment compliance and prevent the emergence of secondary resistance [46,47].

A 9- to 12-month treatment was developed by Armand Van Deun in Bangladesh and helped cure 87.9% of MDR-TB patients in only nine months [48,49]. The efficacy of this treatment might be due to the presence of last-generation fluoroquinolones (moxifloxacin or gatifloxacin) and clofazimine in the combination [37]. This clinical data supports the preclinical data that confirmed the impact of these two molecules on treatment duration in a murine model [50,51]. The short regimen has recently been endorsed by WHO and should be the proposed treatment for each new MDR case without any additional resistance [33]. It is based on a 4- to 6-month initial phase during which the treatment combines kanamycin, moxifloxacin, prothionamide, clofazimine, high-dose isoniazid and ethambutol, and then a 5-month continuation phase without kanamycin, prothionamide and isoniazid.

7.2.3. Surgical treatment

Surgical treatments are sometimes prescribed given the lack of therapeutic options in case of treatment inefficacy or intolerance. Surgical treatments used to be prescribed when antibiotics had not yet been developed. They aim to reduce the bacillary load by resecting major lesions with a high number of bacilli or to prevent hemorrhagic complications [52,53]. The authors of a recent literature review support the use of the surgical procedure in combination with the antibiotic therapy for some patients presenting with MDR-TB and XDR-TB [54]. Elective partial lung resection is now recommended by WHO in the treatment of MDR-TB [33].

7.2.4. Airborne precautions

Airborne precautions are strict and prolonged until sputum smear culture negativity. The treatment of MDR-TB and XDR-TB is more restrictive than the one for TB caused by a susceptible strain. Isolation precaution must be taken to prevent cross-transmission and to increase treatment compliance [55].

8. Conclusion

Multidrug-resistant TB is a real threat. Following several years with no medical progress in that field, the past decade saw the development of many new diagnostic and therapeutic innovations that will help implement a better management of TB patients.

Author contribution

T. Maitre wrote the article.

N. Veziris, A. Aubry, V. Jarlier, J. Robert and CNR-MyRMA reviewed the article.

Disclosure of interest

The laboratory has been supported by Janssen for performing preclinical works on bedaquiline.

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Original article

Influenza B burden during seasonal influenza epidemics in France

Analyse du poids de la grippe B dans les épidémies de grippe saisonnière en France

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Abstract

Context. – Seasonal flu outbreaks are linked to the circulation of influenza virus type A or B. Special attention has always been paid to influenza A epidemics; but recently, several studies have investigated the impact of influenza B virus epidemics, particularly as, since the 1980s, two antigenically different influenza B lineages co-circulate, raising the issue of vaccine matching.

Objectives. – We present the results of influenza B burden during nine influenza seasons (2003–2013) and vaccine matching of the circulating lineages.

Patients and methods. – Clinical and virological influenza surveillance data, collected by the Regional Groups for Influenza Surveillance Network in France, allows for studying the burden of influenza in the practice of the population of ambulatory care physicians.

Results and conclusion. – Our analysis is based on 37,801 samples, of which 12,036 were virologically confirmed influenza cases (31.8%), including 3576 cases of influenza B (29.7% of influenza cases). Influenza B viruses significantly circulated during six seasons. For each season, the influenza B epidemic peaked later than the influenza A epidemic. Influenza B is very common in children of school age but also affects other age groups. Finally, more than one-third of the analyzed influenza B viruses belonged to a different lineage than the one used in the composition of the trivalent vaccine. Our results are comparable to those described in other countries.

Keywords: France; Influenza B; Flu outbreak

Résumé

Contexte. – Une attention particulière a toujours été portée à l'épidémiologie des grippes saisonnières de type A mais récemment, plusieurs études se sont intéressées à l'impact des épidémies liées aux virus de grippe B, et ce d'autant que, depuis les années 1980, deux lignages antigéniquement différents de grippe B co-circulent, posant la problématique de l'adéquation vaccinale.

Objectifs. – Nous présentons ici les résultats concernant le poids de la grippe B au cours de neuf saisons grippales (2003–2013), et l'adéquation vaccinale aux lignages circulants.

Patients et méthodes. – Les données de surveillance clinique et virologique de la grippe, collectées par le Réseau des groupes régionaux d'observation de la grippe en France, permettent d'étudier la problématique de la grippe dans la patientèle des médecins de soins ambulatoires.

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Résultats et conclusion. – Notre analyse repose sur 37 801 prélèvements, dont 12 036 cas de grippe virologiquement confirmés (31,8 %) incluant 3576 cas de type B (29,7 % des cas de grippe). Les virus de grippe B ont circulé de façon notable au cours de six saisons. Pour chaque saison, le pic de circulation des virus de type B a été postérieur à celui des virus de type A. La grippe B est particulièrement fréquente chez les enfants d'âge scolaire, mais touche aussi les autres tranches d'âge. Plus d'un tiers des virus de grippe B analysés appartenait à un lignage différent de celui retenu pour la composition du vaccin trivalent. Nos résultats sont comparables à ceux décrits dans d'autres pays.

Mots clés : France ; Grippe B ; Épidémie de grippe

1. Introduction

Annual seasonal influenza epidemics are linked to the circulation or co-circulation of influenza virus type A (subtypes H3N2 or H1N1) or B [2], posing a public health problem especially because of severe presentations and influenza-related deaths in at risk populations. Healthcare services are overwhelmed and may be disorganized during epidemics, with economic repercussions in terms of loss of productivity [1].

Over the past few decades, research mainly focused on influenza A because of its pandemic potential. Various studies have only recently showed the impact – varied but substantial and stronger than expected – of epidemics caused by influenza B viruses [2–4].

In addition, since the mid-1980s, two antigenically different influenza B lineages (B/Victoria and B/Yamagata) alternatively or simultaneously circulate. This raises the issue of vaccine matching as trivalent vaccines include only one of these lineages. To reduce this risk, manufacturers have been suggesting using quadrivalent seasonal vaccines with two lineages of influenza B viruses for several years now [2,3,5].

The Regional Groups for Influenza Surveillance Network (French acronym GROG) has been contributing to the influenza surveillance in metropolitan France since 1984 by collecting clinical and virological data from patients presenting with acute respiratory tract infection symptoms and consulting at the physician's office. Clinical and virological data of more than 50,000 patients have been collected over time by family physicians (FPs) and pediatricians of the GROG network as part of the influenza surveillance. They were then fed into a database known as "Vircases".

Using this database, we conducted a retrospective analysis as part of a study named "Influenza B in Vircases Database" (IBVD). The study was granted financial support without any expected compensation by GlaxoSmithKline Company, and was conducted by Open Rome. The primary objective of the IBVD study was to describe, during the 2003–2013 influenza surveillance seasons in France, the seasonal distribution, characteristics and clinical symptoms of patients by type of influenza viruses (A and B). The secondary objective was to study vaccine matching for influenza B lineages that circulated during the same period.

We report results on influenza B burden in metropolitan France during nine (2003–13) influenza seasons (excluding the 2009–2010 pandemic season) as well as results pertaining to vaccine matching with the currently circulating lineages. Clinical descriptions have already been published [6].

2. Patients and methods

2.1. Data source: GROG network

Created in 1984, the GROG network is an influenza surveillance and early alert network in outpatient care [7,8] that falls under the French 1901 association law and is a partner of the French National Public Health Agency (French name: Santé publique France). The network consists of FPs and pediatricians (referred to hereinafter as "surveillance physicians") who collect, from October to April, clinical and virological data for the real-time follow-up of influenza in outpatient care. An average of 530 (range 506–608) surveillance physicians took part in the network from 2003 to 2013; 80% of them were FPs. They covered 21 of the 22 regions of metropolitan France.

2.2. GROG network and data collection

Each surveillance physician collects his own healthcare data and nasopharyngeal samples from a portion of patients presenting with a 48-hour history maximum of acute respiratory infection (ARI) suggesting influenza. ARI is defined as the sudden onset of at least one respiratory sign or symptom (cough, rhinitis, coryza, etc.) and of at least one systemic symptom indicative of an acute infection (fever, asthenia, cephalalgia, myalgia, malaise, etc.).

Patients whose samples have been collected are handed out a standardized questionnaire to collect data related to demographics, risk factors justifying influenza vaccination, influenza vaccination status for the ongoing season, clinical signs and symptoms, antibiotic or antiviral drug prescription at the end of the consultation, and whether the patient was referred to hospital following consultation with the surveillance physician.

This data, as well as the virology results, have been captured into the secure Vircases database since 2003. The database has been developed in partnership with Open Rome research company.

2.3. Virological sampling and diagnosis

Every sample, alongside its corresponding questionnaire, is immediately put into a triple packaging as per international regulation on infectious substance transportation. The packages are then sent to the national reference center for Influenzae viruses (Pasteur Institute in Paris and Lyon University Hospital) or to one of the GROG virology laboratories. These laboratories are

tasked with identifying the virus responsible for the patient's ARI. If influenza infection is confirmed, laboratories determine the type and subtype of influenza virus.

From 2003 to 2009, the detection of influenza viruses mainly relied on enzyme immunoassays and on isolation in cell cultures. The identification of the subtype and of the antigenic characterization was performed by national reference centers and relied on hemagglutination inhibition assays using specific polyclonal sera. Laboratory techniques have greatly improved since the 2009–2010 influenza pandemic. They are now mainly based on real-time reverse transcriptase polymerase chain reaction (RT-qPCR); this technique allows for the detection, typing, and sometimes subtyping of type A viruses, and for the determination of type B virus lineage [9,10]. In addition to this molecular detection and as per recommendations issued by WHO collaborative centers, it is now possible to subtype and determine the lineage and variant by hemagglutination inhibition on the isolated virus. This complementary study is only performed on a random subgroup, corresponding to approximately 10% of influenza viruses received by the national reference center.

2.4. Study population

The population included in this analysis was that of the IBVD study. The analysis was based on the description of confirmed virological cases of influenza B included in the Vircases database from 2003 to 2013.

As per IBVD study protocol, exclusion criteria were applied on the Vircases database during data extraction from the study database. Excluded patients included vaccinated patients, patients presenting with a co-infection with two influenza viruses, and cases caused by an influenza type or subtype for which less than 40 cases had been detected during a given season.

As the analysis presented in the current study was based on the description of seasonal influenza epidemics, we incidentally excluded from the IBVD database patients whose age was unknown as well as all cases sampled during the 2009–2010 pandemic because of its peculiar characteristics and non-seasonal nature.

2.5. Statistical analysis

We took into consideration various criteria and definitions.

We used the same age groups as those considered by the European Center for Disease Prevention and Control (ECDC) for the surveillance of influenza and by the GROG network in France: 0–4 years, 5–14 years, 15–64 years and 65 years and above. The epidemic peak was defined, for each type of influenza viruses, as the week with the highest number of detected or isolated influenza cases of this type. The circulation of influenza B viruses is defined as substantial when they represent more than 5% of all influenza viruses isolated or detected during a given season. On the basis of the ECDC definition [11], a type or subtype of circulating influenza virus is defined as dominant when it accounts for more than 60% of all influenza cases during a given season, and as codominant when it accounts for 40–60% of all influenza cases during a given season.

We used median tests and Wilcoxon rank tests to respectively compare medians and age distributions of patients presenting with a virologically confirmed influenza. We compared qualitative variables using Chi-square tests. Significance threshold was set at 0.05 for all tests.

Analyses were performed on Excel and STATA software version 11.2 (STATA Corp., Texas, USA).

2.6. Ethical consideration and consent form

French ethics regulations mention that the oral consent of patients or parents is enough for epidemiological surveillance studies. Each surveillance physician was in charge of collecting the oral consent of patients, which was then written on the standardized questionnaire sent with the swab. As per French laws and regulations, no specific authorization from regulatory authorities was necessary to retrospectively analyze anonymous data collected during routine care when performing routine surveillance.

The limited and controlled access to the GROG network database granted to Open Rome was regulated by a research contract drafted as part of the IBVD study. Data remains the property of the GROG network.

3. Results

A total of 47,132 samples collected by the surveillance physicians of the GROG network and analyzed to identify influenza viruses were included in the IBVD study database from October 2003 to April 2013. As per secondary exclusion criteria defined for this work, 9331 samples (of which 2968 influenza samples) were excluded from the analysis. The present analysis was thus performed on 37,801 samples, of which 12,036 were virologically confirmed influenza cases (31.8%) (Fig. 1). Sample distribution was constant over the nine study seasons (Table 1). Influenza cases were distributed as follows: 8460 type A (4618 A(H3N2), 1457 A(H1N1)pdm09, 952 seasonal A(H1N1) (i.e., before May 2009), 1433 non-subtyped A, and 3576 type B (790 B/Victoria, 1308 B/Yamagata and 1478 undetermined B) (Fig. 1).

Between 2003 and 2013 (excluding the 2009–2010 pandemic), type B influenza viruses accounted for 29.7% of all influenza cases on average, with great discrepancies from one season to another ($\min \leq 5\%$; $\max = 62.3\%$) (Table 1). Influenza B viruses circulated substantially (>5% of all influenza viruses during the season) during six of the nine study seasons. Influenza B was dominant (>60% of all influenza viruses of the season) in 2005–2006 and codominant (40–60% of all influenza viruses of the season) in 2010–2011 and 2012–2013. Influenza B virus was not predominant but still significant in 2007–2008 (34.8% of all influenza cases) and was less frequently observed in 2004–2005 and 2008–2009, accounting for 9.7% and 15.2% of influenza cases respectively (Chart 1).

When influenza B virus substantially circulated, the epidemic always peaked later than the influenza A one, i.e. 4 weeks later on average (range 2–8 weeks). This difference was not major (only 2 or 3 weeks) for the three seasons where influenza B

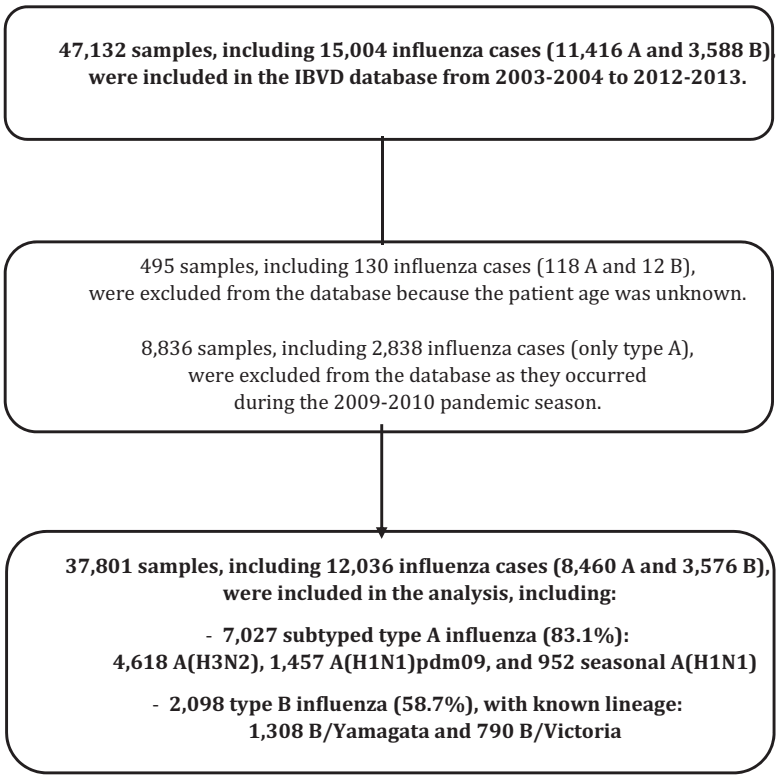

Fig. 1. Study population selection.
Sélection de la population de l'étude.

Table 1
Number of samples and influenza viruses and distribution by influenza type. France, 2003–2004 to 2012–2013 (pandemic season excluded).
Nombre de prélèvements et de virus grippaux et répartition par type de virus grippaux. France, 2003–2004 à 2012–2013 (hors saison pandémique).

Season	Epidemic period (week/year)	Number of samples	Number of influenza viruses	Type A influenza (%)	Type B influenza (%)
2003–2004	47/2003–01/2004	2502	875	100	0.0
2004–2005	03/2005–12/2005	3356	977	90.3	9.7
2005–2006	03/2006–11/2006	4435	844	37.7	62.3
2006–2007	04/2007–08/2007	4140	959	100	0.0
2007–2008	02/2008–08/2008	4583	1249	65.2	34.8
2008–2009	50/2008–07/2009	4288	1381	84.8	15.2
2009–2010	Non-analyzed pandemic season				
2010–2011	51/2010–08/2011	5141	1961	52.6	47.4
2011–2012	05/2012–09/2012	4203	1374	96.3	3.7
2012–2013	51/2012–09/2013	5153	2416	44.9	55.1
Total		37,801	12,036	70.3	29.7

virus was dominant or codominant (2005–2006, 2010–2011 and 2012–2013). However, in 2004–2005, 2007–2008 and 2008–2009, influenza B epidemic peak was reached 4 to 8 weeks after influenza A peak (Table 2).

Influenza B infection affects all age groups, even though school-aged children (5–14 years) are more affected than others (Chart 2). Distribution of type A and B influenza case patients over the study period was significantly different depending on age ($P < 0.01$): patients presenting with influenza B were slightly younger (median = 10 years old) than patients presenting with influenza A (median = 14 years old) ($P < 0.01$). The proportion of type B influenza was more significant in the 5–14 age group (18.1% of study samples that tested positive for type B influenza) than in the other age groups (7.1% of positive samples for type B influenza) ($P < 0.01$) (Chart 2). Targeted data analysis of children aged below 15 years showed that the median age of children presenting with influenza B was significantly higher (median age: 6 years) than that of children presenting with influenza A (median age: 4 years) ($P < 0.01$). The high frequency of influenza B among children aged between 5 and 14 years was observed regardless of the lineage.

However, the impact of influenza B on each age group varied by season. The virus was present in 6.2% to 43.8% of samples collected from children aged between 5 and 14 years presenting with ARI (Chart 3) during the six seasons with a substantial circulation of influenza B virus. Influenza B was also observed,

Table 2
Week of influenza epidemic peak by influenza type. France, 2003–2004 to 2012–2013 (pandemic season excluded).
Semaine du pic épidémique de grippe par type de virus grippal. France, 2003–2004 à 2012–2013 (hors saison pandémique).

Season	Epidemic period (week/year)	Week of epidemic peak[a] for type A influenza viruses	Week of epidemic peak[a] for type B influenza viruses	Number of weeks between epidemic peaks of type A and B influenza
2003–2004	47/2003–01/2004	47	[b]	
2004–2005	03/2005–12/2005	5	10	5
2005–2006	03/2006–11/2006	5	7	2
2006–2007	04/2007–08/2007	5	[b]	
2007–2008	02/2008–08/2008	4	8	4
2008–2009	50/2008–07/2009	3	11	8
2009–2010	Non-analyzed pandemic season			
2010–2011	51/2010–08/2011	2	5	3
2011–2012	05/2012–09/2012	7	[b]	
2012–2013	51/2012–09/2013	5	7	2

[a] Defined as the week with the highest number of isolated or detected influenza viruses.
[b] No substantial circulation of type B influenza virus (<5% of virological confirmations of the season).

even though irregularly and with a lesser intensity, in the other age groups: in individuals aged 65 years and above, influenza B accounted for 2.2% (1/46) to 20.9% (32/153) of collected samples depending on the seasons.

Both lineages of influenza B (Yamagata and Victoria) simultaneously circulated during the whole study period. We observed that the proportion of influenza B viruses for which the lineage was available was on average 58.7%, ranging from 29.7% in 2010–2011 to 74.8% in 2012–2013. The Yamagata and Victoria lineages were detected every season of the six seasons where influenza B virus substantially circulated. They respectively accounted for 62.5% and 37.5% of all influenza B cases for which the lineage was available. One lineage was however more predominant than the other every season. Both lineages, Yamagata and Victoria, were each predominant during three seasons: Yamagata in 2004–2005, 2007–2008 and 2012–2013; Victoria in 2005–2006, 2008–2009 and 2010–2011. A mismatch between the dominant circulating influenza B lineage and the lineage included in the seasonal influenza vaccine was observed during three of the six study seasons (2005–2006, 2007–2008 and 2008–2009). For one of this season, type B influenza virus was dominant (2005–2006) (Chart 4). Over the six seasons with a substantial circulation of influenza B virus, influenza B cases associated with a mismatched strain accounted for 38% of influenza B cases for which the lineage was available.

4. Discussion

Access to data collected by the GROG network and extracted for the IBVD study purpose helps in describing influenza B burden on outpatient care during seasonal epidemics in metropolitan France.

Influenza B viruses substantially circulated from 2003 to 2013 and contributed to the burden of influenza epidemics during six of the nine winter seasons (excluding the 2009–2010 pandemic season).

Influenza B burden was quite significant during the nine seasons studied as 9.5% of patients who consulted at the physician's office for acute respiratory symptoms and who had a nasopharyngeal swab performed presented with influenza B, versus 22.4% of patients presenting with influenza A. Influenza B thus accounted for approximately one-third (29.7%) of all influenza cases studied. Data from other countries describes a similar impact of type B viruses within all documented influenza cases, with 29% in the Netherlands between 1992 and 2007 [12], 24% in the United States between 2001 and 2011 [2], 26% in Finland between 1999 and 2012 [3], and 22.6% in the analysis of data available since 2000 in 26 countries of both hemispheres [4].

When influenza B viruses substantially circulated during our study period, its relative proportion within each seasonal influenza epidemic varied by years. It accounted for 9.7% (2004–2005) to 62.3% (2005–2006) of analyzed influenza viruses. This great difference was also observed in the above-mentioned studies as well as in a literature review performed by Paul Glezen et al. [13].

Although influenza B viruses usually circulate alongside type A viruses, these latter viruses are most often predominant. Over the nine seasons of our study, type B viruses only had a greater impact than influenza A viruses (>60% of influenza viruses of the season) or a comparable impact as influenza A viruses (40–60% of influenza viruses of the season) during three seasons: 2005–2006, 2010–2011 and 2012–2013.

For the six seasons when influenza B viruses substantially circulated, the viral detection peak was always posterior to that of type A viruses. This "second wave" of influenza B thus extended the influenza circulation period. A Brazilian study reported a similar chronology [14].

Similar to studies conducted in other countries, our study results show that influenza B is observed among all age groups [2], even though more frequently affecting children [4] and especially school-aged children (5–14 years age group in our study) [3]. Median age of patients consulting for influenza B (10 years) is statistically lower than that of patients consulting for influenza A (14 years) [4]. However, this tends to reverse when restricting the analysis to children aged under 15 years, for whom median age for confirmed influenza B (6 years) is

significantly higher than that of children presenting with influenza A (4 years) [2].

Similar to what happened in other countries, both type B lineages (Yamagata and Victoria) simultaneously circulated during seasons associated with a substantial circulation of influenza B viruses. A discrepancy between the dominant influenza B lineage and the lineage included in the seasonal influenza vaccine was observed during three of the six study seasons, especially during the only season where influenza B was dominant. During the study period, type B viruses of a different lineage than the one recommended for the vaccine accounted for 38% of influenza B cases for which the lineage was available. This figure is similar to the one reported in Finland (41.7%) between 1999 and 2012 [3]. Our study did not allow for an analysis of the potential clinical impact of these mismatches.

Although assessing several seasons and based on many samples, our study has a few limitations. A selection bias might have occurred considering that the choice of patients to sample was left to physicians. This bias is, however, limited by the use of a clear case definition and by the comparison with other ARI case patients sampled in similar conditions. In addition, several associated factors tend to lead to an excessive representation of children in our data set: 20% of physicians from the GROG network are pediatricians and thus, they only sample children. Children are more likely to consult than adults and to be sampled when presenting with ARI. Vaccinated individuals, mostly adults aged over 65 years, were excluded from the database. As influenza B is quite frequent in children, this excessive representation of children in the database could lead to overestimate influenza B burden.

Conversely, two factors could have contributed to underestimating influenza case patients, and mainly influenza B during the study period. Influenza viruses were still circulating during some seasons when the surveillance was stopped mid-April. This mainly concerned influenza B viruses as they usually circulate a few weeks after type A viruses. Finally, virological diagnostic methods improved during the study period. Enzyme immunoassays and cultures were mainly used before the 2009–2010 pandemic [15], and a more sensitive technique, RT-qPCR, then became the reference method in France [16]. The number of detected influenza viruses may thus have been more frequently underestimated before the pandemic than after. However, the issue of virological diagnostic method improvement is as important for type A viruses as for type B viruses.

Overall, influenza B is not harmless as we observed that it accounted for almost 10% of winter consultations for acute respiratory infection and for 29.7% of virologically confirmed influenza case patients. Influenza B even accounted for 60% of all influenza case patients observed during the 2005–2006 season. Influenza B is particularly frequent in school-aged children (5–14 years) but also affects other age groups. Finally, more than a third of influenza B viruses observed in France during the study period belonged to a different lineage than the one included in the trivalent vaccine. This brings a potential support to the use of the quadrivalent vaccine.

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Contributors

J.M.C., A.M. and I.D. designed the study.

J.M.C., A.M., I.D., E.N. and T.T.B. implemented the study.

A.M. and I.D. analyzed the data.

S.V.D.W., B.L. and H.F. contributed to performing and interpreting virological analyses.

A.M. and I.D. wrote the article.

A.M., I.D., J.S.C., M.R., C.B., E.N., T.T.B., H.F., B.L., S.V.D.W. and J.M.C. reviewed and approved the final version of the article.

Disclosure of interest

A.M. and J.M.C.: conference – one-off invitation as speaker or attendee. Employed by a firm which received subventions from the study promoter (GlaxoSmithKline) and other pharmaceutical laboratories involved in the field of influenza.

I.D., E.N. and T.T.B.: employed by a firm which received subventions from the study promoter (GlaxoSmithKline) and other pharmaceutical laboratories involved in the field of influenza.

S.D.V.W.: member of the European Scientific Working Group on Influenza (ESWI).

B.L.: conference – one-off invitation as speaker or attendee (subvention received from GlaxoSmithKline and Roche). Member of the European Scientific Working Group on Influenza (ESWI).

The authors J.S.C., M.R., C.B. and H.F. declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medmal.2016.11.006.

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Original article

Lactobacillus bacteremia: Pathogen or prognostic marker?

Bactériémie à Lactobacillus *: pathogène ou marqueur pronostique ?*

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Abstract

Objective. – *Lactobacillus* bacteremia is a rare event and its epidemiology is poorly known. Whether *Lactobacillus* bacteremia is a contaminant, a risk factor, or a risk marker of death remains an open question.

Patients and methods. – We conducted a retrospective study of patients presenting with *Lactobacillus* bacteremia (LB), between January 2005 and December 2014, at the Grenoble University Hospital.

Results. – LB was observed in 38 patients (0.34% of all positive blood cultures). Cancer (40%), immunosuppression (37%), and use of central venous devices (29%) were frequently associated with LB. We observed a significant increase with time in the number of *Lactobacillus* positive blood cultures among all blood cultures performed ($P = 0.04$). LBs were divided into two clinical-biological presentations: secondary bacteremia with a known portal of entry ($n = 30$) and isolated bacteremia ($n = 8$). Case fatality was 31% at D28, 55.2% at 1 year in the secondary bacteremia group, and 12.5% (both at D28 and 1 year) in the isolated bacteremia group. Secondary bacteremia with a known portal of entry was significantly associated with case fatality after adjustment for age, co-infection, cancer, immunosuppression, diabetes, and sex (OR 14.9 [1.04–216] $P = 0.047$) for fatality at one year, but not for D28 fatality ($P = 0.14$).

Conclusion. – *Lactobacillus* bacteremia may be an important marker of disease severity rather than a pathogen, suggesting comorbidities. It should not be considered a contaminant, but should lead physicians to screen for associated infections and underlying diseases.

Keywords: *Lactobacillus*; Bacteremia

Résumé

Objectif. – Les bactériémies à *Lactobacillus* (BL) sont rares et leur épidémiologie est mal connue. Le débat sur la pathogénicité des lactobacilles reste ouvert, notamment de savoir s'ils représentent un marqueur de fragilité ou s'ils sont pathogènes.

Patients et méthodes. – Étude rétrospective de janvier 2005 à décembre 2014 auprès des patients présentant une BL au centre hospitalo-universitaire de Grenoble.

Résultats. – Nous avons retrouvé 38 cas (0,34 % de l'ensemble des flacons d'hémocultures positifs). Les patients présentaient les facteurs suivants : cancer (40 %), immunodépression (37 %), voie veineuse centrale (29 %). L'incidence des flacons positifs pour lactobacilles au sein de l'ensemble des hémocultures réalisées a augmenté significativement avec le temps ($p = 0,04$). Les BL ont été réparties en deux groupes : infection d'organe ($n = 30$) et bactériémie isolée ($n = 8$). La létalité était plus importante en cas d'infection d'organe (31 % à j28 et 55,2 % à 1 an) que de bactériémie isolée (12,5 % à j28 et 1 an). Le caractère localisé de l'infection (versus bactériémie isolée) était significativement associé au décès dans un model multivarié ajusté pour l'âge, le sexe, les co-infections, la présence d'un cancer, de diabète ou d'une immunosuppression (OR 14,9 [1,04–216] $p = 0,047$) pour la mortalité à 1 an mais pas pour la mortalité à 28 jours ($p = 0,14$).

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Conclusion. – Les BL sont un marqueur de gravité plus qu'un pathogène, démasquant la fragilité des patients. Les BL ne sont pas des contaminants mais leur présence doit conduire à la recherche de co-infections et de pathologies sous-jacentes.

Mots clés : Lactobacillus ; Bactériémie

1. Introduction

Lactobacilli are Gram-positive, facultative anaerobic, rod-shaped bacteria. They are present in the gastrointestinal tract and the vagina. *L. paracasei* and *L. casei* are used as probiotic treatments for vaginal candidiasis and diarrhea [1]. The mortality, epidemiology, and pathogenicity of *Lactobacillus* bacteremia (LB) are still unclear. Only five longitudinal cohort studies were published on LB: a recent Taiwanese cohort study of 89 patients with only half of them receiving appropriate antibiotic treatment [2], a cohort study of 28 patients with a focus on *L. rhamnosus* infections only (16 case patients) [3]; a cohort study of 15 patients, mostly pediatric [4]; a series of 45 patients admitted to the intensive care unit [5], and a comprehensive analysis of LB case patients in the whole population of Finland between 1990 and 2000 [6]. Several case reports were also published, with a high proportion of infective endocarditis (IE). Recent epidemiological data indicates an increase in LB reported cases after 2008. Data on morbidity and mortality is scarce in published cohort studies and mainly comes from case report-based reviews with conflicting results. Despite the above data, whether lactobacilli are contaminant, risk factors, or risk markers of death remains an open question. We performed a 9-year retrospective analysis of LB case patients at Grenoble University Hospital to update our knowledge of the epidemiology and outcome of LB patients.

2. Patients and methods

2.1. Case patients at the Grenoble University Hospital

LB was identified by the Bacteriology Laboratory. Patients' epidemiological and medical data was obtained from archived medical files (digitalized as of 2004). We collected medical history, infection site, number of positive blood cultures, associated infections, antibiotic susceptibility, and cardiac ultrasonography. We also assessed case fatality at Day 28 (D28) and at one year.

2.2. Bacterial identification and antibiotic susceptibility testing

Blood samples were collected in BACTEC® aerobic and anaerobic media (Becton Dickinson, Pont de Claix, France), which were incubated in the BACTEC 9240® system (from 2005 to 2010) and in the BACTEC FX® system thereafter. Blood cultures were incubated at 35 °C for five days. We performed Gram-staining and subculture of positive samples on 5% sheep blood agar plates (bioMérieux, Marcy l'Étoile, France) incubated at 37 °C in aerobic and anaerobic conditions. The isolated bacterial strains were identified with the API 50 CH L® system (bioMérieux) according to the manufacturer's recommendations. *Lactobacillus* "species" was considered as the final result when biochemical identification was deemed "unacceptable" on the basis of these recommendations.

Antibiotic susceptibility testing was performed using the Kirby-Bauer technique according to recommendations issued by the antibiogram committee of the French microbiology society (French acronym CA-SFM) for penicillin G (PEN), amoxicillin (AMX), cefalotin (CF), cefotaxime (CTX), imipenem (IMP), gentamicin (GM), chloramphenicol (C), doxycycline (DO), erythromycin (E), pristinamycin (PTN), rifampin (RAM), cotrimoxazole (SXT), ofloxacin (OFX), and vancomycin (VAN).

2.3. Risk factor definition

We chose to classify predisposing risk factors as suggested by Salvana et al. [7]:

- diabetes (for patients on antidiabetic treatment);
- immunosuppression (including chemotherapy for neoplasia within two weeks of LB diagnosis, current immunosuppressive therapy, AIDS);
- active neoplasm (defined by active treatment or remission within six months);
- central venous device implanted before bacteremia (any delay);
- recent upper respiratory tract or digestive surgery or digestive endoscopy (both upper and lower tracts).

Bacteremia was considered isolated in the absence of clinical, biological, or radiological evidence of specific organ involvement. It was otherwise considered a "secondary bacteremia with a known portal of entry" (SB), with a specific category for infective endocarditis. Finally, antibiotic treatment was considered appropriate if active against all microorganisms, on the basis of the antibiotic susceptibility testing.

2.4. Statistical analysis: STATA 12 and R software

We used Chi^2 test to compare categorical variables, and data was presented as numbers and percentages. Student's *t*-test was used to compare continuous variables with a normal distribution and data was presented as mean ± standard deviation. Wilcoxon test was used in case of non-normal distribution, with data expressed as median [1st–3rd quartile]. Linear regression with time was performed for the ratio of positive *Lactobacillus* blood

cultures over total blood cultures, as well as linear regression with time for the ratio of positive *Lactobacillus* blood cultures over any-bacterium positive blood culture. A multivariate logistic regression was used to evaluate the impact of epidemiological characteristics on fatality (polymicrobial status, sex, isolated bacteremia or not, above-mentioned risk factors), and fatality at Day 28 and one year. An alpha risk significance threshold of 5% was used.

3. Results

3.1. Epidemiology

We analyzed 543,765 blood culture bottles (BCB) sampled between 2005 and 2014; 35,857 (6.6%) of which were positive for bacteria. *Lactobacillus* species was observed in 121 positive blood cultures (0.34% of positive BCBs). Those 121 BCBs were sampled from 38 patients. The linear regression with time of the ratio of *Lactobacillus* positive BCBs over total BCBs showed a significant increase with time ($P = 0.04$; from 6/46,706 in 2005 to 19/60,515 in 2014), but the regression with time of the ratio of *Lactobacillus* positive BCBs over any-bacterium positive BCBs did not reach a significant level ($P = 0.07$; from 6/2,817 in 2005 to 19/4,092 in 2014).

Demographic characteristics are listed in Table 1. Median age was 60 [48–71] years, with 56% of male patients. Thirty-one (82%) LB positive patients presented with at least one risk factor, most frequently immunosuppression, cancer, or implanted central venous device. Overall, 39% of patients presented with two or more risk factors. We did not observe any difference in terms of risk factors among the various types of LB (Tables 1 and 2). No patient underwent endoscopy, and surgery was mainly digestive with only one pharynx surgery.

LBs were mainly SBs (76% of cases): 45% were urinary and digestive tract infections and 39% were pulmonary infections. Isolated bacteremia was not rare (24%). Only one patient presented with a confirmed infective endocarditis [8].

LBs were associated with a very high case fatality at D28 (23.7%) and at 1 year (45%). The one-year case fatality was higher in the SB group than in the isolated bacteremia group (55.2% vs. 12.5%; $P = 0.021$). We did not observe any difference at D28 (12.5% vs. 31% $P = 0.23$) (Tables 1 and 2). The multivariate logistic regression analysis for the risk of death, adjusted for polymicrobial status, age, cancer, immunosuppression, diabetes, and sex revealed that the type of infection (SB versus isolated bacteremia) showed significant association between LB and case fatality at one year (OR 14.9 [1.04–216], $P = 0.047$), but not with case fatality at D28 (OR 9.48 [0.47–192], $P = 0.14$).

Table 1
Statistical data of the 38 patients presenting with *Lactobacillus* bacteremia.
Données statistiques des 38 patients ayant présenté une bactériémie à Lactobacillus.

Epidemiological characteristics	Median (%)	Interquartile (number)
Total	38	
Male (%, *n*)	58%	22
Age in years (median, interquartile)	60	[48; 71]
Type of infection (%, *n*)		
Isolated bacteremia	23.7%	9
Endocarditis	2.6%	1
Localized infection	73.7%	28
Pulmonary	39.3%	10
Urinary and digestive tracts	42.9%	12
Venous thrombosis	14.3%	4
Other	7.1%	2
Comorbidity (%, *n*)		
Surgery or endoscopy	18.4%	7
Immunosuppression	36.8%	14
Neoplasia	39.5%	15
Central venous catheter/access port	28.9%	11
Diabetes	21.1%	8
Probiotic use	5.3%	2
One or more comorbidity	81.6%	31
≥ 2 comorbidities	42.1%	16
Cardiac ultrasonography (%, *n*)		
Positive	2.6%	1
Negative	47.4%	18
Not performed	50.0%	19
Outcome (%, *n*)		
Death	44.7%	17
Early death ($\leq$1 month)	26.3%	10
Late death, 1-12 months (for patients alive after 30 days, $n = 26$)	18.4%	7
Recurrences (for patients alive after 30 days, $n = 28$)	21.4%	6
1-year case fatality in the localized infection group	57.1%	16
1-year case fatality in the isolated bacteremia group	11.1%*	1
Antibiotic treatment duration in days, median (interquartile)		
All case patients 33 available data among 38 patients	15	[14–24.5]
Single bacterium 12 available data among 5 patients	14	[10–15]
Polymicrobial 21 available data among 23 patients	21**	[14–28]

Values are presented as percentage (number) for qualitative variable, and mean (standard deviation) for continuous variable. Recurrence analysis was performed for 28 patients (patients who died in the first 30 days following bacteremia were excluded).
* $P = 0.016$ versus localized infection group.
** $P = < 0.04$ versus single bacterium.

3.2. Microbiological data

Microorganisms associated with LB are listed in Table 2. Overall, 56% of patients presented with polymicrobial infections. Polymicrobial infections occurred significantly more often in the SB group (71% vs. 20%, $P = 0.005$). Species were identified in only 46% of cases; the most frequent species being *L. rhamnosus* ($n = 9$) and *L. paracasei* ($n = 3$).

3.3. Antibiotic treatment

Antibiotic treatment was prescribed according to the identified bacterium and antibiotic susceptibility for all patients

Table 2
Clinical data of 238 patients presenting with *Lactobacillus* bacteremia between 2005 and 2014 at Grenoble University Hospital.
Données cliniques des 38 patients ayant présenté une bactériémie à Lactobacillus *entre 2005 et 2014 au centre hospitalo-universitaire de Grenoble.*

Year	Age	Sex	Clinical symptoms	Predisposing factors	LB-associated infection	Positive bottles at first occurrence	Species	Other microorganisms	Antibiotics	Antibiotic treatment duration (days)	Cardiac ultrasonography	Outcome
2005	60	M	Fever, abdominal pain	Thymectomy, radiotherapy, diabetes	Digestive infection	3	*L. delbrueckii*	*S. epidermidis*[a]	NA	NA	NA	Surgery, recurrence, and death at M9 (abdominal infection)
2006	84	F	Fever, respiratory distress	Central venous catheter	Aspiration pneumonia	1	*L. paracasei*		NA	NA	Negative	Death at D14 (respiratory failure)
2006	36	M	Fever, respiratory distress	AIDS	Pulmonary abscess	1	*L. paracasei*	*C. glabrata*[a], *E. faecalis*[a]	Amoxicillin, voriconazole clindamycin, ofloxacin	42	Negative	Cured
2007	48	M	Fever, respiratory distress	Cirrhosis	Aspiration pneumonia	1	*L.* spp.	*Aerococcus*[a]	Piperacillin-tazobactam	14	NA	Cured
2007	52	F	Melena	Retroperitoneal liposarcoma, access port	Digestive infection	1	*L. salivarius*		Piperacillin-tazobactam, fluconazole	14	Negative	Death at M4 (therapeutic limitation)
2008	52	F	Fever, respiratory distress	Diabetes	Aspiration pneumonia	1	*L. plantarum*		Piperacillin-tazobactam	NA	NA	Death at D2 (respiratory failure)
2009	57	F	Sepsis	Hepatic graft, tacrolimus	Liver abscess	5	*L. rhamnosus*	*P. aeruginosa*[a], *E. hirae*[a], *S. epidermidis*[a], *Bacillus pumilus*[a], *C. tropicalis*[a], *C. glabrata*[a]	Cefepime, colistin, caspofungin, tobramycin, linezolid	56	Negative	Death at D22 (multiple organ failure)
2009	43	M	Septic shock	Leiomyosarcoma, chemotherapy with daunorubicin and dexrazoxane, access port	Venous thrombosis infection	3	*L.* spp.	*K. pneumoniae*[a], *Veillonella* spp.[a], *S. epidermidis*[a], *S. salivarius*[a], *C. glabrata*[a]	Piperacillin-tazobactam, ciprofloxacin	28	NA	Recurrence and death at M3 (sepsis)
2010	43	M	Fever, respiratory distress	Pharynx cancer, surgery and radiotherapy, access port	Aspiration pneumonia	2	*L. rhamnosus*		Ceftazidime, ornidazole, ciprofloxacin, fluconazole	28	Negative	Cured
2010	23	F	Abdominal pain	Anorexia	Digestive infection	2	*L.* spp.	*E. faecium*[a], *Pediococcus*[a]	Piperacillin-tazobactam	NA	NA	Death at D1 (sepsis)
2010	77	M	Fever, hip pain [7]	Cured prostate cancer	Infective endocarditis	3	*L. paracasei*		Amoxicillin, gentamicin	42	Positive	Recurrence and cardiac surgery

Table 2 (*Continued*)

Year	Age	Sex	Clinical symptoms	Predisposing factors	LB-associated infection	Positive bottles at first occurrence	Species	Other microorganisms	Antibiotics	Antibiotic treatment duration (days)	Cardiac ultrasonography	Outcome
2010	60	M	Severe sepsis	Primitive myelofibrosis becoming acute, chemotherapy with cytarabine and mitoxantrone	Isolated bacteremia	1	*L.* spp.	*Streptococcus oralis*[a]	Piperacillin-tazobactam, vancomycin	21	NA	Death at D27 (respiratory failure)
2010	60	F	Isolated fever	Acute myeloid leukemia, central venous catheter	Isolated bacteremia	1	*L.* spp.		Imipenem, metronidazol	14	NA	Recurrence at D25 and then cured
2010	78	M	Fever, respiratory distress	Multiple dental surgery, central venous catheter	Pneumonia	1	*L. casei*	*S. epidermidis (bronchial endoscopy), C. glabrata (bronchial endoscopy)*	Meropenem, ciprofloxacin, fluconazole, vancomycin	14	NA	Cured
2010	32	F	Isolated fever	Leiomyosarcoma and metastasis, PICC line	Venous thrombosis infection	3	*L. rhamnosus*,	*C. glabrata*[a]	Ertapenem	56	Negative	Three recurrences
2011	58	M	Septic shock	Diabetes	Fournier gangrene	1	*L. acidophilus*	*C. glabrata*[a]	Imipenem	42	Negative	Cured
2011	79	M	Chills	Diabetes, stomach surgery 2 days before	Isolated bacteremia	1	*L.* spp.		Piperacillin-tazobactam	14	Negative	Cured
2011	71	F	Fever, asthenia	Kidney graft, tacrolimus, azathioprine	Isolated bacteremia	1	*L.* spp.	*Bifidobacterium* spp.[a]	Amoxicillin	21	Negative	Cured
2012	68	F	Isolated fever	Breast cancer, metastasis, access port	Venous thrombosis infection	2	*L.* spp.	*S. epidermidis*[a], *K. pneumoniae*[a], *C. glabrata*[a]	NA	NA	NA	Death at M6 (therapeutic limitation)
2012	70	F	Fever, respiratory distress	Anorexia, LV5FU2, cisplatin, digestive neoplasia	Aspiration pneumonia	1	*L. rhamnosus*	*S epidermidis*[a], *Stenotrophomonas* (bronchial endoscopy), *C. glabrata* (bronchial endoscopy)	Ticarcillin-clavulanic acid, ciprofloxacin, co-trimoxazole, caspofungin	15	Negative	Death at D8 (respiratory failure)
2012	48	M	Fever, abdominal pain	Cirrhosis, hepatic carcinoma	Digestive infection	1	*L.* spp.		Piperacillin-tazobactam	14	NA	Death at D27 (therapeutic limitation)
2012	60	F	Isolated fever	Sarcoidosis, corticosteroids, access port	Isolated bacteremia	1	*L.* spp.		No antibiotic	NA	Negative	Cured
2012	86	F	Fever, abdominal pain	None	Isolated bacteremia	1	*L.* spp.		Cefpodoxime	15	NA	Cured
2012	86	F	Septic shock	None	Nephritis	1	*L.* spp.	*E. coli*[a]	Amoxicillin-clavulanic acid	15	NA	Cured
2012	77	M	Fever, respiratory distress	Myeloma, melphalan, corticosteroids, thalidomide	Pneumonia	1	*L.* spp.		Ceftriaxone, levofloxacin	10	NA	Cured

Table 2 (*Continued*)

Year	Age	Sex	Clinical symptoms	Predisposing factors	LB-associated infection	Positive bottles at first occurrence	Species	Other microorganisms	Antibiotics	Antibiotic treatment duration (days)	Cardiac ultrasonography	Outcome
2012	40	M	Fever, abdominal pain	Gastric surgery (sleeve)	Spleen abscess	2	*L. rhamnosus*	*C. glabrata* (abscess surgery), *E. faecalis* (abscess surgery)	Imipenem, metronidazol	15	Negative	Recurrence at M4 and M9, and then cured
2013	53	M	Vomiting	Gastric tumor, 5-FU, oxaliplatin, access port, artificial nutrition	Access port thrombosis	1	*L.* spp.		Amoxicillin	5	NA	Death at M3 (tumor progression)
2013	64	M	Abdominal pain, fever	Hepatic transplantation, tacrolimus, MMF	Hepatic abscess	5	*L. rhamnosus*	*E. faecalis*[a]	Ertapenem	21	NA	Recurrence at M2 and then cured
2013	54	F	Abdominal pain, fever	Cardiac transplantation, cyclosporine, MMF	Isolated bacteremia	1	*L.* spp.		Amoxicillin	10	Negative	Cured
2013	70	M	Isolated fever	Spleen and pancreas ablation for kidney tumor metastasis	Isolated bacteremia	2	*L. rhamnosus*		Amoxicillin	10	NA	Cured
2013	33	M	Hemolytic uremic syndrome	Lymphoma	Pneumonia	2	*L. rhamnosus*	*E. faecium*[a], *S. haemolyticus*	Piperacillin-tazobactam, vancomycin	15	Negative	Death at D7
2013	68	F	Isolated fever	Diabetes, hemodialysis	Sacrum abscess	1	*L.* spp.	*E. faecalis*[a], *E. cloacae*[a]	Imipenem	28	NA	Death at M2 (pneumonia)
2014	44	M	Septic shock	Cirrhosis	Pneumonia	4	*L.* spp.	*E. faecalis* (bronchial endoscopy)	Imipenem	4	Negative	Death at D4
2014	63	F	Fever, acute kidney graft injury	Kidney transplantation (tacrolimus, MMF), type 1 diabetes	Nephritis	4	*L.* spp.	No	Amoxicillin-clavulanic acid	15	Negative	Cured
2014	77	M	Septic shock	Kidney cancer, type 2 diabetes	Angiocholitis	3	*L. rhamnosus*	*Streptococcus anginosus*[a]	Piperacillin-tazobactam	14	Negative	Death at M6 (pneumonia)
2014	85	M	Hemorrhagic stroke		Pneumonia	2	*L.* spp.	*Citrobacter braakii* (bronchial endoscopy)	Amoxicillin-clavulanic acid	9	No	Death at D26 (pneumonia recurrence)
2014	66	M	Fever, abdominal pain	Pancreas cancer, access port, gemc-itabine + oxaliplatin	Angiocholitis	5	*L.* spp.	*Staphylococcus epidermidis*[a]	Imipenem, amikacin	14	No	Death at M2 (cancer)
2014	68	M	Fever, chill, abdominal pain	Type 2 diabetes	Angiocholitis	1	*L.* spp.	*E. faecalis* and *Staphylococcus haemolyticus* (peritoneal fluid)	Piperacillin-tazobactam, amikacin	21	Negative	Cured

NA: non-available data.

[a] Microorganism identified in blood culture.

but four. Antibiotic treatment data was not available for four patients, and one patient did not receive any treatment. Treatment duration was longer for polymicrobial infections than for single bacterium infections ($P = 0.04$), with a median of 21 [14–28] versus 14 [10–15] days. *Lactobacillus* susceptibility was good for amoxicillin, macrolides, rifampicin (90% of cases), and imipenem (87%). Susceptibility was 70% for gentamicin, < 50% for cephalosporin and vancomycin, and < 10% for fluoroquinolones. All patients with available data received an antibiotic active against both *Lactobacillus* and the associated microorganisms (one patient was treated with cefpodoxime for a *Lactobacillus* infection susceptible to ceftriaxone on the basis of laboratory test).

4. Discussion

We observed a higher frequency of risk factors in our study population (82%) than in two articles based on case reports (45 and 47%) [9,10]. The incidence of LB observed in our study before 2008 was close to Salminen's data [6]. We observed an increase in the number of case patients after 2008, as in Gouriet's study, with a more than two-fold increase in LB incidence [6]. This increase was not due to a contamination process or to an increased number of blood culture analyses as the linear regression of *Lactobacillus* BCBs over whole BCBs was significant. However, the increase in LB number was dependent upon the overall increase in bacteremia number. This may reflect the increasing number of patients with predisposing factors for bacteremia and LB, e.g., a higher survival rate for patients presenting with cancer and/or immunosuppression, or an increasing use of central venous devices (the main risk factor). Another explanation, although controversial, may be the increasing use of probiotics believed to be associated with LB. However, Salminen et al. [6] addressed this question and did not report any increase in LB case patients between 1990 and 2000, while probiotic consumption increased exponentially during this period. Finally, the authors of a recent monocentric survey [11] reported a minimal risk of infection among hospitalized patients consuming probiotics compared to other hospitalized patients. Altogether these results suggest that probiotics are harmless for healthy patients, but they should be used with caution in patients presenting with preexisting risk factors. The global prevalence of LB observed in other articles conducted with specific populations [4,12] ranged from 0.2 to 0.4%.

We observed a high overall fatality for LB patients and a high rate of early death (< 30 days after LB identification). SB was associated with one-year fatality even after adjustment for known risk factors for death in infectious disease, but it was not associated with fatality at D28, which was rather due to infections. Our hypothesis was that *Lactobacillus*-associated bacteremia could be the indicator of a severe status rather than a pathogen per se. It could therefore be a risk marker for comorbidities. Arguments in favor of this hypothesis are a high prevalence of mixed infections associated with *Lactobacillus*; a high prevalence of underlying diseases in LB patients (mainly cancer and immunosuppression); a lower virulence of isolated LB; and early death despite an effective antibiotic treatment. We believe LB to be a significant negative prognostic marker. A multivariate analysis carried out in a larger population-based study is necessary to confirm this hypothesis. The size of our study limits the available statistical power of the multivariate analysis, and may explain the absence of association between SB and case fatality at D28.

The case fatality observed in our study was higher than that observed in case report-based reviews (22–23% [7,9]), but consistent with cohort study data (40%) [2,4]. The rates of SB, IE, and isolated LB are consistent with cohort study results [4], but not with case report-based reviews. This may be due to a case selection bias (greater number of IE in published case reports and reviews).

The distribution of *Lactobacillus* species is difficult to determine. Our results are consistent with those of the five major publications [2–4,7,9] representing 439 lactobacilli altogether. The most frequent lactobacilli are *L. rhamnosus* ($n = 74$), *L. casei* ($n = 72$), *L. paracasei* ($n = 32$), *L. acidophilus* ($n = 22$), *L. salivarius* ($n = 22$), *L. plantarum* ($n = 21$), and *L. fermentum* ($n = 20$). However, as in our study, species identification was often lacking ($n = 126$) and specific analyses must be performed to investigate the various virulence levels between species.

Very few studies focused on *Lactobacillus* infection treatment [2,4,7,9]. Glycopeptide susceptibility is related to the fermentative status of *Lactobacillus* strains: heterofermentative strains such as *L. rhamnosus* are naturally resistant to vancomycin whereas homofermentative strains such as *L. acidophilus* are not. Glycopeptides must not be used empirically as *L. rhamnosus* is frequently isolated. Fluoroquinolones should not be considered because of the emergence of a high resistance rate which had not been described before 2005. We also observed a lower aminopenicillin resistance than previously described [9], confirmed by other recent data [2]. There is currently no consensus on antibiotic treatment for LB, not even for IE, in the European Society of Cardiology consensus [13]. Published data suggests using high doses of aminopenicillin and gentamicin for IE. In other cases, the choice should be made according to associated bacterial infections. The empirical treatment for a Gram-positive bacillus bacteremia with SB may be ureidopenicillin and clavulanic acid or carbapenem, which already proved to be associated with a high susceptibility rate (> 85%) [2] (due to frequent co-infections with anaerobic and Gram-negative bacilli). Considering the high rate of co-infections, amoxicillin-clavulanic acid may be used as an empirical treatment so as to cover any other bacteria until confirmation of the isolated bacteremia by cultures. Furthermore, a systematic fungal culture is required due to frequent co-infection with *Lactobacillus* sp. Antibiotic treatment duration is difficult to determine and must be based on the severity of the infection and its localization.

Lactobacillus bacteremia is a rare but increasingly frequent infection. Secondary bacteremia with a known portal of entry seems to be more severe than isolated bacteremia. It seems to be a negative prognostic marker related to patient's comorbidities rather than a pathogen per se. Although isolated bacteremia is extremely rare, it may lead to death and IE with severe valvular damages. *Lactobacillus* should therefore not be systematically considered as a contaminant, but should lead physicians to

screen for associated infections and underlying diseases (e.g., gynecological or digestive cancers). A broad-spectrum antibiotic treatment should be initiated in case of secondary bacteremia with a known portal of entry because of frequent co-infections.

Disclosure of interest

The authors declare that they have no competing interest.

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Authors' contribution

BF designed the study, collected data, and wrote the article.
PF collected bacteriological data and wrote the bacteriological methods.
TJ performed the statistical analysis.
PM contributed to writing the article.
IP contributed to collecting bacteriological data.
JPB reviewed the article.
PP designed the study and contributed to writing the article.

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Original article

Bacterial chondritis complications following ear piercing

Chondrites bactériennes de l'oreille post-piercing

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Abstract

Background. – Body piercing has become widespread and is associated with increased complications. Post-piercing chondritis may lead to severe residual deformity. We aimed to report case patients presenting with post-piercing chondritis in our department and to describe clinical features and treatment.

Patients and methods. – We conducted a retrospective study of patients presenting with post-piercing chondritis in the infectious disease department of Tenon Hospital, Paris, France.

Results. – We included 21 patients. Fifteen bacteriological cultures were positive (7 *Pseudomonas aeruginosa*, 5 *Staphylococcus aureus*, and three other). Dual intravenous antibiotic therapy was administered to 13 patients for a median duration of six days [2–8], replaced by an oral antibiotic therapy for a median duration of 15 days [7–40]. Eight patients received oral antibiotic monotherapy for 10 days [7–30]. Median duration of antibiotic therapy was 16 days. Earring removal was performed for 18 patients. No ear deformity or general complication was reported.

Conclusion. – Transcartilaginous ear piercing may lead to infectious complications or deformity. In case of chondritis, early administration of an antibiotic therapy active against *P. aeruginosa* and *S. aureus* is recommended. Specific guidelines are needed.

Keywords: Chondritis; Piercing; *Pseudomonas aeruginosa*

Résumé

Introduction. – Le piercing est une pratique devenue très courante et s'accompagne d'une augmentation de ses complications. Les chondrites *post-piercing* peuvent aboutir à des déformations séquellaires de l'oreille. Nous rapportons les cas de patients ayant présenté une chondrite *post-piercing* et décrivons leurs caractéristiques et leur prise en charge.

Patients et méthodes. – Nous avons mené une étude rétrospective au sein du service de maladies infectieuses et tropicales de l'hôpital Tenon, Paris, France.

Résultats. – Vingt et un patients ont été inclus. Quinze prélèvements bactériologiques étaient positifs en culture (7 *Pseudomonas aeruginosa*, 5 *Staphylococcus aureus* et trois autres). Une double antibiothérapie intraveineuse était administrée pour 13 patients pendant une durée médiane de six jours [2–8], relayée par une antibiothérapie orale pour une durée médiane de 15 jours [7–40]. Pour huit patients, une monothérapie antibiotique était prescrite pour 10 jours [7–30]. La durée médiane de l'antibiothérapie pour l'ensemble des patients était de 16 jours. Le retrait du bijou était réalisé chez 18 patients. Aucune déformation séquellaire ou complication générale n'était constatée.

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Conclusion. – Les piercings du cartilage de l'oreille peuvent se compliquer d'infection locale ou de déformation inesthétique. En cas de chondrite, le traitement antibiotique doit être administré précocement et doit être actif sur *Pseudomonas aeruginosa* et *Staphylococcus aureus*. Des recommandations consensuelles sont souhaitables.

Mots clés : Chondrite ; Piercing ; *Pseudomonas aeruginosa*

1. Introduction

Body piercing has become widespread since the last decade [1]. Ear piercing is usually performed in jewelry stores or tattoos studios and has to be done in strict sanitary conditions. Local and general complications resulting from body ornamentation are well-known [2,3] and consist in healing disorders and infectious complications. Infectious complications are observed in up to 25% of piercing procedures [4].

Transcartilaginous ear piercing is the third most common site for body piercing, excluding the ear lobe [5,6], and is associated with a higher risk of infectious complications [7]. Several sites are used for cartilage piercing (Fig. 1). Cartilage trauma, even after a minor trauma such as piercing [8], can lead to chondritis or perichondritis. These infections could be much more severe because of the avascular condition of cartilage which increases bacterial development [9] and reduces the efficacy of antibiotics.

Patients also have to be cautious for a longer period of time following procedure, including the period of cartilage healing which is longer compared with other anatomical areas (6 to 8 weeks) [10].

Bacteria involved in this type of infections may also be different from the usual bacteria involved in skin infections such as *Streptococcus* and *Staphylococcus aureus* (*S. aureus*). In a recent systematic published review [11], *Pseudomonas aeruginosa* (*P. aeruginosa*) accounted for a majority of chondritis case patients and first-line oral antibiotics did not target the cultured bacterium in 50% of cases. Thus, 92.3% of the pretreated population had to be hospitalized.

Fig. 1. Ear cartilage piercing sites.
Sites anatomiques de piercing du cartilage de l'oreille.

Early diagnosis and appropriate antibiotic therapies are necessary to prevent unsightly scars and local or general complications. However, healthcare professionals are poorly trained and lack standardized guidelines to adequately manage piercing infectious complications.

Chondritis complications following ear piercing have dramatically increased over the past years and to our knowledge few reports have been published [11,12].

We aimed to describe post-piercing ear chondritis complications among patients managed in our infectious disease department. Epidemiological, medical, and antibiotic therapy data was collected during the follow-up period.

2. Materials and methods

We identified the codes corresponding to piercing chondritis using the Infectious and Tropical Disease Department database (DIAMM G, Nancy, France). We retrospectively collected demographic, bacteriological, and previous treatment data for each participant.

Bacteriological analysis was performed using semi-quantitative methods. Bacteriological samples were collected using swabs or suction syringes in aseptic conditions. Aerobic and anaerobic cultures were performed on Columbia agar technique (bioMérieux, Craponne, France). All patients provided written informed consent before photos were taken.

3. Results

We included 21 patients from January 2010 to May 2015: 20 female patients and one male patient, with a mean age of 22 years [16–35]. All piercings had been performed by professional piercers. Four patients had previous complications related to another piercing (data available for 14/21 patients). Three patients reported atopic dermatitis and four patients had a medical history of dermatitis. None of them was diabetic and 50% (7/14) were current smokers. Nonsteroidal anti-inflammatory drugs were administered to 3/14 patients before the complication event.

Fourteen piercings were performed in the helix and seven in the tragus. Mean time between piercing procedure and symptom onset was 11.5 days [2–1305], with a median interval of seven days [1–152] between symptom onset and diagnosis.

Fig. 2. Chondritis at diagnosis and after 7 days of antibiotic therapy (patient 5).
Chondrite au diagnostic puis après 7 jours d'antibiothérapie (patient 5).

All patients presented with local red patches, swelling, pain, and purulent exudate (Figs. 2 and 3). The median temperature was 37 °C [36.4–40 °C] and two patients had a temperature > 38 °C.

Results are summarized in Table 1.

3.1. Bacteriological data

Twenty participants had at least one bacteriological sample collected. Fifteen of them (75%) were positive 16 to 24 hours after incubation and five were sterile. Among positive samples, 13 out of 15 isolated a single bacterium (7 *P. aeruginosa*, 5 *S. aureus*, and 1 *Staphylococcus epidermidis*) and two isolated several bacterial species (Table 2). Six out of seven *P. aeruginosa* had a wild phenotype and one was resistant to fosfomycin. One out of five *S. aureus* had a wild phenotype and four were resistant to erythromycin, including two penicillinase-producing strains. No patient had a positive blood culture. Five patients had received empirical antibiotic therapy before bacteriological tests (Table 2).

Fig. 3. Chondritis at diagnosis and after completion of antibiotic therapy (patient 7).
Chondrite au diagnostic puis à l'issue de l'antibiothérapie (patient 7).

3.2. Therapeutic care

Thirteen patients (62%) required inpatient hospitalization with a mean length of hospitalization of 5.2 days (median 5 days, range 2–9 days). Earring removal was performed in 17/21 patients (81%).

Initial intravenous antibiotic therapy was administered to 13/21 patients (62%) for a median duration of six days [2–8], corresponding to the duration of the dual therapy. Patients were then switched to oral antibiotic therapy for a mean duration of 15 days [7–40]. Eight patients out of 21 received oral antibiotic therapy (pristinamycin) as a monotherapy for a mean duration of 10 days [7–30]. Overall, the mean duration of antibiotic therapy was 16 days [7–43].

No patient underwent surgery.

3.3. Outcome

Five patients (24%) had local complications (minor scars). No cauliflower ear, keloid, or other unsightly deformities were reported. No general complication occurred.

4. Discussion

To our knowledge we reported the largest series of chondritis complications occurring after piercing.

Our cohort showed a predominant causality of *P. aeruginosa* and *S. aureus* for documented chondritis (87%) similar to other published case reports [10,11]. Five bacteriological samples were sterile due to previous antibiotic therapy for patients 10 and 20 (Table 1).

S. aureus is a skin saprophyte usually involved in cutaneous infectious complications. By contrast, *P. aeruginosa* is a Gram-negative aerobic bacterium commonly involved in otitis and mastoiditis, especially in diabetic patients because of ear moisture. Surprisingly, in our study, the prevalence of *S. aureus* and *P. aeruginosa* was quite similar suggesting a lack of piercer training rather than a lack of post-piercing self-administered care. First-line antibiotic drugs should be effective against these bacteria.

However, none of the isolated bacteria was resistant to fluoroquinolones suggesting that ciprofloxacin may be recommended as a first-line treatment even if it is not recommended without bacteriological identification. Ciprofloxacin has a bactericidal activity and an excellent oral bioavailability (70–80%). It is also associated with substantial tissue penetration [13]. Considering local and general complications, antibiotic therapies should be modified secondarily according to the bacteriological identification. Antibiotic therapy modifications were performed for each patient according to clinical presentations. Treatment also took into consideration the delay between diagnosis and bacterial initial inoculum.

Dramatic outcomes have been published, such as infective endocarditis [14] or toxic shock syndrome [15], mostly due to

Table 1
Summary of included patients.
Synthèse des patients inclus.

Patient number	Age	Sex	Time between piercing and symptom onset (day)	Time between symptom onset and diagnosis (day)	Piercing site	Cultured bacteria	Hospitalization	Piercing removal	Intravenous antibiotics	Total antibiotic therapy duration	Sequelae
1	22	F	4	3	Helix	NA	Yes	Yes	Yes	31	Yes
2	27	F	32	10	Helix	Few *P. aeruginosa* colonies	Yes	Yes	Yes	35	Yes
3	18	F	4	12	Helix	Many *P. aeruginosa* colonies	Yes	Yes	Yes	21	No
4	19	M	2	2	Helix	Few *P. aeruginosa* colonies	Yes	Yes	Yes	15	No
5	29	F	24	11	Helix	Few *P. aeruginosa* colonies	Yes	Yes	Yes	21	No
6	30	F	7	3	Helix	Many *P. aeruginosa* colonies	Yes	Yes	Yes	16	NA
7	16	F	23	31	Helix	Few *Enterobacter cloacae* and *S. aureus* colonies	Yes	Yes	Yes	27	NA
8	17	F	7	23	Tragus	Sterile	Yes	Yes	No	10	Yes
9	25	F	1305	3	Helix	Many GABHS and *S. aureus* colonies	Yes	Yes	Yes	23	No
10	21	F	61	152	Tragus	Cutaneous flora	No	Yes	No	7	No
11	18	F	26	4	Tragus	Many *S. aureus* colonies	No	No	No	10	NA
12	19	F	NA	NA	Helix	Many CoNS colonies	No	No	No	15	NA
13	26	F	4	15	Helix	Many *P. aeruginosa* colonies	Yes	Yes	Yes	28	NA
14	29	F	16	2	Tragus	Sterile	No	Yes	No	15	NA
15	19	F	24	25	Helix	Many *S. aureus* colonies	No	No	No	8	NA
16	21	F	33	8	Helix	Few *S. aureus* colonies	Yes	No	Yes	40	Yes
17	22	F	NA	NA	Tragus	Sterile	No	Yes	No	7	No
18	23	F	NA	7	Tragus	Few *P. aeruginosa* colonies	No	Yes	No	30	NA
19	28	F	3	1	Tragus	Many *S. aureus* colonies	Yes	Yes	Yes	12	No
20	20	F	3	5	Helix	Sterile	Yes	Yes	Yes	16	NA
21	35	F	2	3	Helix	Many *S. aureus* colonies	Yes	Yes	Yes	30	Yes

NA: not available; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus;* GABHS: group A beta-hemolytic streptococci; CoNS: coagulase-negative staphylococci

Table 2
Empirical antibiotic therapy administered before bacteriological samples.
Antibiothérapies empiriques administrées avant les prélèvements bactériologiques.

Patient number	Antibiotic administered before sampling	Bacteria cultured
7	Pristinamycin	*Staphylococcus aureus* *Enterobacter cloacae*
9	Amoxicillin-clavulanic acid	*Staphylococcus aureus* Group A *Streptococcus*
10	Topical fusidic acid	Cutaneous flora
12	pristinamycin Topical fusidic acid	*Staphylococcus epidermidis*
20	Doxycycline	Sterile culture

delayed antibiotic therapy or immune deficiency of the host. However, as published in a series of chondritis case patients reported regardless of etiology, no patient had a positive blood culture [8]. This might be explained by the avascular condition of the cartilage or the early patient management. Similarly, no life-threatening condition was observed in our cohort, which might be explained by early and adequate treatment initiation. Only 5 out of 12 recovered patients presented with sequelae (small papules no more than one centimeter).

Antibiotic therapy was also associated with hygiene care to increase its efficacy. Jewelry should be removed as soon as possible to insure whole-site sterilization. We added impregnated alcoholic dressing for its anti-inflammatory and antiseptic properties as well as to avoid patient handling.

Piercing complications are increasingly being reported [16]. This suggests that preventive measures may be the best way to avoid such complications.

Medical and medication history should be adequately taken prior to piercing. Individuals describing atopic dermatitis or contact dermatitis due to allergy to metal are at higher risk of infectious disease complications [17]. Three patients of our cohort had atopic dermatitis and four had allergic contact dermatitis. Titanium jewelry, usually used by piercers, seems to reduce local allergy.

Additional health conditions such as current smoking or comorbidity treatments may increase the risk of complications because of delayed skin healing. Seven patients of our study were current smokers and three were on treatment (2 isotretinoin and 1 solifenacin), which induced severe xerosis. This population may need to pay more attention to post-piercing care. Nonsteroidal anti-inflammatory drugs must also be avoided.

Piercing guns are associated with a higher risk of cartilage trauma compared with other techniques. Sterile needles minimize the risk of complications; their use is therefore recommended although a previous human cadaver histological study did not show significant results [18].

Professional piercers should provide clear advice to candidates for piercing, and clients should seek early medical attention. Post-piercing ear chondritis usually occurs within 2 to 4 weeks of the procedure but the whole healing time may reach eight weeks for cartilage. This time period is crucial to avoid infectious complications.

Additionally, post-piercing care must be performed carefully and until complete cartilage healing. Most of our patients had not correctly performed post-piercing care and thus presented with bacterial infection.

Antiseptic solution for post-piercing care must be effective on causal bacteria. Fisher et al. reported *P. aeruginosa* chondritis case patients due to contaminated bottle of benzalkonium chloride provided by piercers [7]. This antiseptic solution, routinely used, is ineffective against PA.

A decree issued in 2008 now regulates piercing procedure in France and has mandated good practice training for piercers. This legal framework is still lacking in several countries. In our opinion, such decree is necessary to improve awareness of piercers, customers, and healthcare professionals.

We recommend administering early dual antibiotic therapy including ciprofloxacin because of the avascular condition of the cartilage and the high prevalence of *P. aeruginosa* and *S. aureus*. The second antibiotic drug must be a beta-lactam active against *P. aeruginosa* such as ceftazidime or aztreonam in case of allergy. For local care, we recommend early jewelry removal and local application of povidone-iodine or chlorhexidine solutions.

Our study has limitations. We did not manage to measure the prevalence of infectious complications in cartilaginous ear piercing because of our retrospective analysis and because data was missing. Prospective studies are needed. One is currently undergoing in our department.

5. Conclusion

Transcartilaginous ear piercing is an invasive procedure and may lead to infectious complications or unsightly deformity. Patients should be fully informed and advised to consult a medical practitioner in case of local complications. First-line antibiotics should be administered early and be active against *P. aeruginosa* and *S. aureus*. Prospective studies and guidelines for healthcare professionals are needed.

Author contribution

All authors extensively contributed to the work.

G. Bellaud, G. Pialoux, and A. Canestri made substantial contributions to the study conception and design, data acquisition, analysis, and interpretation.

G. Bellaud, G. Pialoux, A. Canestri, and L. Slama drafted the article or reviewed it for intellectual content and final approval of the version to be published.

G. Bellaud, S. Gallah, M. Merlant, S. Cousseau, and MG. Lebrette contributed to clinical data collection.

Disclosure of interest

The authors declare that they have no competing interest.

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Original article

Predictors of mortality among HIV-infected children receiving highly active antiretroviral therapy

Facteurs prédictifs de mortalité chez les enfants infectés par le VIH sous traitement antirétroviral hautement actif

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Abstract

Background and objectives. – The mortality rate of HIV-infected children can be reversed under highly active antiretroviral therapy (HAART). The impact of HAART on the mortality of HIV-infected children in Cameroon has not been extensively documented. We aimed to measure the mortality rate of HIV-infected children under HAART and to identify predictive factors of mortality.

Methods. – Retrospective cohort study of 221 children initiated on HAART from 2005 to 2009 and followed-up until 2013. Survival data was analyzed using Kaplan Meier method and Cox regression model to identify independent predictors of child mortality on HAART.

Results. – Overall, 9.9% of children ($n = 22$) died over a follow-up period of 755 child-years (mortality of 2.9 per 100 child-years); 70% of deaths occurred during the first six months of HAART. The probability of survival after four years of treatment was 88.7% (95% CI = [84.2–93.3]). During the multivariate analysis of baseline variables, we observed that the WHO clinical stages III and IV (HR: 3.55 [1.09–13.6] and HR: 7.7 [3.07–31.2]) and age ≤ 1 year at HAART initiation were independently associated with death (HR: 2.1 [1.01–5.08]). Neither orphanhood, baseline CD4 count or hemoglobin level nor low nutritional status predicted death in this cohort.

Conclusion. – The mortality of children receiving HAART was low after five years of follow-up and it was strongly associated with WHO stages III and IV and a younger age at treatment initiation.

Keywords: Children; HIV; HAART; Cameroon

Résumé

Contexte et objectifs. – La mortalité des enfants infectés par le VIH peut être inversée sous traitement antirétroviral hautement actif (TAHA). L'impact du TAHA sur la mortalité de ces enfants est faiblement rapporté au Cameroun. L'objectif était de mesurer le taux de mortalité des enfants infectés par le VIH traités par TAHA et les facteurs prédictifs de mortalité.

Méthodes. – Analyse de cohorte rétrospective sur 221 enfants ayant démarré le TAHA entre 2005 et 2009, et ayant été suivis jusqu'en 2013. Utilisation de la méthode de Kaplan-Meier et du modèle de Cox pour l'analyse de survie et pour l'identification des facteurs prédictifs de décès sous TAHA.

Résultats. – Parmi les 221 enfants, 9,9 % ($n = 22$) sont décédés au cours d'une période de suivi de 755 enfants-années (mortalité : 2,9 pour 100 enfants-années). Soixante-dix pour cent des décès sont survenus durant les six premiers mois de TAHA. La probabilité de survie après quatre ans de traitement était de 88,7 %. En analyse multivariée, les stades cliniques OMS 3 et 4 et l'âge ≤ 1 an à l'initiation du traitement étaient indépendamment associés au risque de décès. Le statut d'orphelin, le taux de CD4 et d'hémoglobine et le statut nutritionnel n'étaient pas prédicteurs de décès dans cette cohorte.

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Conclusion. – La mortalité sous TAHA était faible à 60 mois de suivi et fortement associée aux stades OMS 3 et 4 et au très jeune âge à l'initiation du TAHA.

Mots clés : Enfants ; VIH ; Traitement antirétroviral hautement actif ; Cameroun

1. Background

Approximately 3.3 million children under 15 years of age were living with HIV by the end of 2012. Most of them (90%) were from Sub-Saharan Africa. Only 650,000 of them were receiving highly active antiretroviral therapy (HAART) in low- and middle-income countries [1]. The benefit of early HAART on the survival and quality of life of HIV-infected children has been widely documented in historical cohorts of HIV-infected children from Western countries and Asia [2–5]. Mortality under HAART in Africa remains, on the other hand, quite high especially during the first six months following HAART initiation [6–8]. Many factors have been incriminated in the high mortality of HIV-infected children under treatment in Africa: poor nutritional status, WHO clinical stage, anemia, social and demographic data including maternal deaths. Cameroon is an endemic country for HIV. Access to HAART for infants has, however, been improved and almost 5000 HIV-infected children have been initiated on HAART from 2005 to 2013 (among 39,000 eligible patients) [9]. This national cohort is mainly being followed in four or five sites nationwide despite efforts for decentralization. In addition, the level of retention in care and the mortality rate on HAART is unknown. We aimed to measure the survival rate of children receiving HAART in Cameroon and to identify associated factors of child mortality in a pediatric antiretroviral therapy (ART) clinic.

2. Methods

2.1. Study site and population

We performed the study in the ESSOS Hospital of Yaoundé, Cameroon. This approved treatment center for ART is one of the two main pediatric ART clinics of the city. Pediatric HAART progressively started to be administered in this center as of the early 2000s. The program was then enhanced from 2005 onwards with the access to HAART free of charge nationwide. A total of 450 children have been initiated on HAART in this center since the start of the program.

2.2. Study design and data collection

We conducted a retrospective cohort study to analyze the survival rate and associated factors among children initiated on HAART between 2005 and 2009. Inclusion criteria included age ≤ 17 years, HIV-infected status on HAART, treatment initiation no later than January 2009, and patients still had to be followed at the study site. A total of 19 patients were excluded as they were transferred to another hospital. We included 221 children out of 450 (Fig. 1). Biological and clinical data at baseline and during follow-up were extracted from the clinical files. The primary endpoint was the rate of child mortality.

2.3. Clinical and biological procedures for follow-up and antiretroviral guidelines

Monthly follow-ups were scheduled for children receiving HAART during the first three months of treatment. Follow-up consultations were then scheduled quarterly. HAART was free of charge from the hospital pharmacy and was delivered on a monthly basis. Clinic services during the follow-up period were paid by patients. A supportive compliance program was offered to parents and children > 8 years of age. Early infant diagnosis using either real time PCR or qualitative PCR was performed at six weeks and later confirmed after nine months assuming a six week-delay following weaning for breastfed infants. The final diagnosis was established after 15 months. The final confirmation of the patient's HIV-negative status during the follow-up period was confirmed based on the following criteria: one negative virological test plus one negative serological test at or after 12 months, with a six week-delay following weaning for breastfed children. HIV infection was confirmed by two positive PCR at any time during follow-up, irrespective of the feeding mode, or by one positive serological test after 15 months.

2.4. Guidelines for antiretroviral treatment initiation followed in the study

The preferred first-line regimen for HIV-1-infected children and infants was non-nucleoside reverse-transcriptase inhibitors (NNRTIs) consisting of two nucleoside reverse-transcriptase inhibitors (NRTIs) and one NNRTI. The protocol was free of protease inhibitors assuming the mother did not receive any preventive treatment for mother-to-child transmission of HIV during pregnancy. Otherwise a protease inhibitor (PI)-based regimen was initiated. Efavirenz was the preferred NNRTI in children > 3 years of age, whereas nevirapine was prescribed to younger children. HAART was initiated during the follow-up period for all confirmed HIV-infected children < 1 year of age or classified as WHO stage III or IV irrespective of CD4 cell count.

2.5. Data collection

Data was routinely collected at the beginning of the follow-up period. A standard checklist was used for recording information from patient files into a form. The collection form included sociodemographic data, clinical and biological data at baseline

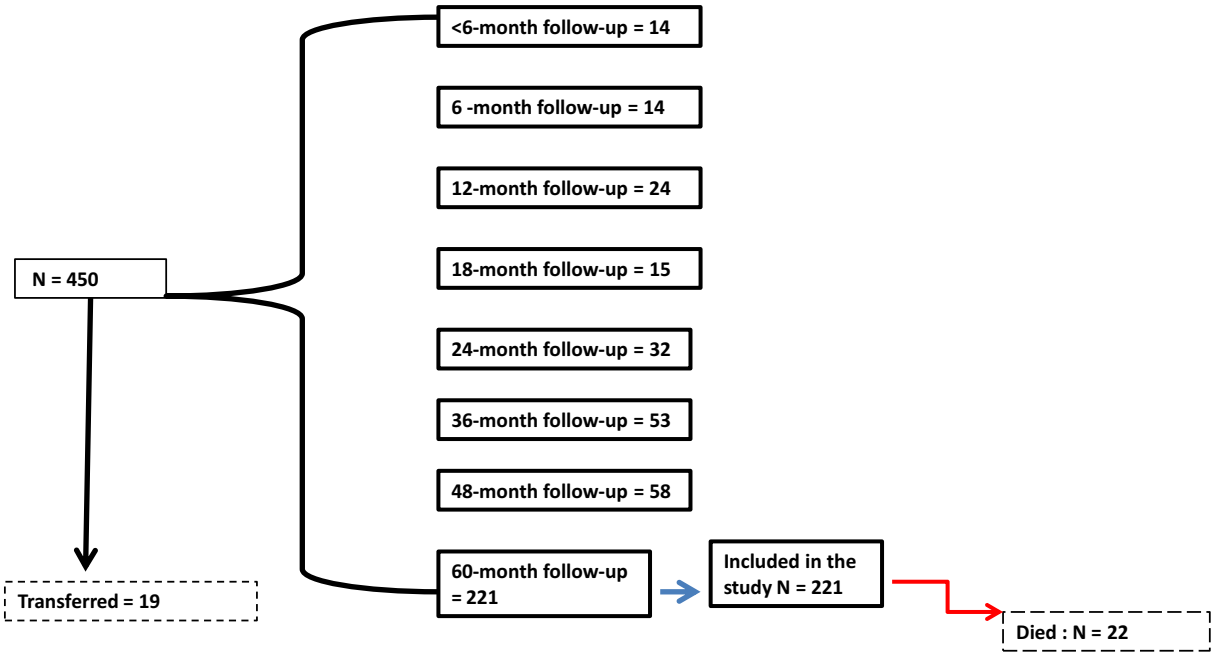

Fig. 1. Flow chart of the open cohort of HIV infected children receiving HAART by duration of follow-up.
Diagramme descriptif de la cohorte de patients pédiatriques infectés par le VIH sous traitement antirétroviral hautement actif par durée de suivi.

and then every six months. Death events were family reported or recorded during hospitalizations. All completed checklists were submitted during the data collection phase for approval of the main investigator. He/she had to check for completeness, coherence, and accuracy. Data was entered into the R3.0 software for analysis.

2.6. Statistical analysis

Participants' characteristics were described using the median with their quartiles, and proportions for qualitative variables. Months or years of follow-up were calculated using the time between HAART initiation and death. Child survival and associated factors were analyzed using Kaplan-Meier analysis method and log-rank test. Factors associated with death were assessed using a Cox model in univariate and multivariate analyses.

2.7. Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of the study center. Informed written consent was obtained from parents at inclusion for care. Information collected from the patients' charts were kept strictly confidential and anonymous.

3. Results

3.1. Baseline cohort characteristics

A total of 221 study participants (children ≤ 17 years) were included in the analysis. The sample comprised 102 females (46%) and 119 males (54%). Almost one third of them (83/221, 37%) were orphans. The youngest child at inclusion was 1.5 months old and the oldest one was 191 months old. The median age at HAART initiation was 36 months (IQR [7.5–74 months]), and almost 1 in 3 (30%) children had started treatment prior to their first birthday. Advanced clinical stages were observed in 1 in 2 children (56%) at enrollment. The median follow-up time was 48 months (IQR [36–60]). However, the median follow-up time was shorter among children who died (2.5 months [IQR 0.5–10.5]). The median level of CD4 cell count was 13.9% at inclusion (IQR 8–21) and the proportion of anemia defined as hemoglobin < 8 g/dl was < 10%. Approximately 9 in 10 participants (197/221, 89%) were receiving a first-line HAART regimen. Table 1 shows the baseline characteristics of this cohort and the survival outcome.

3.2. Survival pattern of the cohort

Of the 221 children followed up on HAART we recorded 22 deaths (9.9%). The most frequent causes of death were sepsis ($n = 5$), respiratory tract infection ($n = 5$), tuberculosis ($n = 4$), encephalopathy ($n = 3$), malnutrition ($n = 3$), Kaposi's sarcoma ($n = 2$), and anemia ($n = 1$). Among the recorded deaths, 68.2% were registered during the first six months of treatment (probability of survival at six months: 92.8% (95% CI = 89.4–96.4). The mortality rate was 2.9 per 100 child-years given the 755 child-years of follow-up. The survival analysis showed a lower probability of survival in children presenting with WHO clinical stages III and IV at HAART initiation, compared with clinical stages I and II (log-rank test; *P*-value 0.005) (Fig. 2).

3.3. Predictors of mortality

In the univariate analysis children with WHO stages III and IV were more likely to die than patients presenting with

Table 1
Baseline characteristics of HIV-infected children at HAART initiation by outcome.
Caractéristiques initiales des enfants infectés par le VIH à l'initiation du traitement antirétroviral hautement actif selon le devenir.

Characteristic	*n* (%)	Outcome	
		Alive, *n* (%)	Dead, *n* (%)
Gender			
Female	102 (44)	90 (45)	12 (55)
Male	119 (56)	109 (56)	10 (45)
HAART protocol			
1st line	197 (89)	177 (89)	20 (91)
2nd line	24 (11)	22 (11)	2 (9)
Orphan			
No	138 (62)	123 (62)	15 (68)
Yes	83 (38)	76 (38)	7 (32)
WHO clinical stage			
Stage 1	47 (21)	44 (22)	3 (14.3)
Stage 2	50 (23)	50 (25)	0 (0)
Stage 3	82 (37)	73 (37)	9 (42)
Stage 4	42 (19)	32 (16)	10 (47)
Weight for age			
<-2Z-score	71 (32)	64 (32)	7 (32)
≥ -2Z-score	150 (68)	135 (68)	15 (68)
CD4 cell count			
$<15\%$	127 (57)	116 (58)	11 (50)
$\geq 15\%$	94 (43)	83 (42)	11 (50)
Hemoglobin level			
<8 g/dl	20 (9)	18 (9)	2 (9)
≥ 8 g/dl	201 (91)	181 (91)	20 (91)
Age at HAART initiation			
≤ 1 year	67 (30)	56 (28.1)	11 (50)
≤ 2 years	22 (10)	21 (10.6)	1 (4.5)
≤ 5 years	46 (21)	41 (20.6)	5 (22.7)
>5 years	86 (39)	81 (40.7)	5 (22.7)

WHO clinical stages I and II (HR [95% CI] = 3.8 [1.0–14.7] to 9.7 [2.6–37.8]); in addition, infants younger than one year at HAART initiation were more likely to die than their older counterparts (HR: 2.1 [1.0–5.0]). In the multivariate analysis, these same factors were independently predicting death (Table 2). Neither hemoglobin level nor CD4 cell count or low nutritional status (weight for age ≤ -2 Z-score) were found to be predictors of death in this cohort.

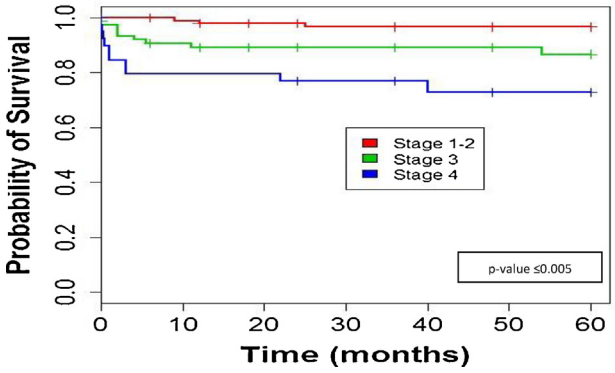

Fig. 2. Probability of survival of HIV-infected children receiving highly active antiretroviral therapy in the pediatric clinic of the Essos Hospital, Yaoundé, Cameroon.
Probabilité de survie des enfants infectés par le VIH sous traitement antirétroviral hautement actif au centre hospitalier d'Essos, Yaoundé, Cameroun.

4. Discussion

Less than 10% (9.9%) of HIV-infected children receiving HAART died during a follow-up period of 755 child-years. The mortality rate was 2.9 deaths per 100 child-years. These findings are consistent with previous data reported in the Democratic Republic of Congo [10,11] and suggest a better outcome than the one observed in infected children on treatment in Kenya [12]. In addition, our mortality rate is similar to the one reported in Malawi in a population followed for a median time of 2.3 years, with almost 10% of children dying [13]. Results from studies conducted outside of Africa for a similar period of time are similar to our findings, with a two-year follow-up mortality rate of 2.8 per 100 child-years reported in Northern Thailand in severely immunosuppressed children with a median CD4 cell count around 5% at HAART initiation [14]. With regard to the previous reports our results are consistent with the low mortality rate recorded in rural Ethiopia among children receiving HAART [15]. Altogether, our mid-term mortality rate is quite satisfactory when compared with other African observational cohorts. It is, however, disappointing when compared with European cohorts [4]. Our study results confirm a high mortality during the first six months of treatment

Table 2
Predictors of death in HIV-infected children receiving HAART in the pediatric clinic of Essos Hospital.
Facteurs prédictifs de décès chez les enfants infectés par le VIH sous traitement antirétroviral hautement actif au Centre Hospitalier d'ESSOS.

Co-variable	Univariate			Multivariate		
	Hazard ratio (HR)	CI (95%)	*P*-value	HR	CI (95%)	*P*-value
Gender	0.753	[0.3–1.7]	0.5			
2nd line HAART	0.87	[0.2–3.7]	0.8			
Orphan	0.54	[0.21–1.40]	0.21			
WHO stage 3	3.86	[1.01–14.77]	0.03	3.55	[1.09–13.62]	0.03
WHO stage 4	9.7	[2.64–37.8]	≤ 0.001	7.7	[3.07–31.2]	0.001
≤ 1 year at HAART initiation	2.3	[1.05–6.2]	0.02	2.1	[1.01–5.8]	0.01
Z-score ≤ -2	0.61	[0.19–1.88]	0.39			
Hemoglobin level	0.89	[0.69–1.14]	0.35			
CD4 cell count %	0.99	[0.96–1.03]	0.87			

as reported by many studies conducted in Africa [11,16,17]. The main baseline characteristics predicting mortality in this cohort were the advanced clinical stages of HIV infection classified as WH0 stages III and IV and age ≤ 1 year at HAART initiation. Advanced clinical stages of HIV infection have been associated with an increased mortality rate in many African cohorts. Deaths occurring around the beginning of treatment may be caused by opportunistic infections or other comorbidities that can hamper recovery despite HAART initiation [18–20]. The authors of Ethiopian, Nigerian, and South African studies report that advanced clinical stages compromise early survival in HIV-infected children [21–23], especially in children with impaired immune status. Early initiation of HAART prior to immunodeficiency has been recommended as a gold standard since 2010 to address this early mortality rate after HAART initiation [23]. In addition, younger age (< 3 years) has been reported as a risk factor; this tendency is supported by the hypothesis that in the absence of routine early diagnosis of HIV infection younger symptomatic children might be expressing the profile of HIV rapid progressors. The rate of both moderate and severe malnutrition observed in this cohort was half lower than previously reported in Africa [21]. Nutritional status was also not predictive of death following HAART initiation compared with other studies conducted in Africa. This difference may be due to the uncomplicated status of our malnourished children allowing prompt initiation of HAART, which is known to reverse life-threatening outcomes in malnourished children [24]. Anemia was not identified as a predictor of death in this study but our analysis may have been limited by the low number of children with Hb level < 7 g/100 ml, a threshold used in many reports [21]. We can postulate that the threshold of 8 g/100 ml retained in our study may have limited the detection of association between mortality and anemia. However, anemia was not a predictor of mortality neither in the South African Sinikithemba cohort nor in the Democratic Republic of Congo [11]. Although severe immunodeficiency is reported to predict death [25–27], CD4 cell count was not recorded as a predictor of death in our cohort; similar findings have been reported in South Africa. In this latter study the chosen threshold for CD4 cell count was 5% (compared with 15% in our study) and was not predicting survival [28]. We acknowledge many limitations for this study, especially missing data and variables that could have been included in the model: measurement of compliance with the HAART regimen, uptake of co-trimoxazole, type of families, and HIV status of the caregiver [29,30]. All children included in our study were considered perinatally infected; this assumption may have limited the identification of the specific survival modalities of perinatally acquired HIV infections as compared with infections related to sexual behavior. Additional studies are therefore required to further analyze predictors of mortality, especially among adolescents.

This study shows the effectiveness of HAART in HIV-infected children. However, we acknowledge that the model and variables retained for analysis were incomplete. Missing data from our study may be considered in a future prospective study.

5. Conclusion

The mortality rate at 60 months of follow-up was 9.9% in one single referral site in Yaoundé, with WHO clinical stages III and IV and age ≤ 1 year at treatment initiation identified as the main independent predictors of death. This mortality rate urges us to extend the use of HAART in HIV-infected children. This may be done by increasing access to early HIV diagnosis at all entry points of care, followed by immediate initiation of HAART according to a "test and treat" approach. A close follow-up is also required during the first six months of HAART to ensure treatment success, especially in infants aged < 1 year at treatment initiation.

Author contributions

A.E.N.N. and B.L. designed the study.
B.L. performed the analysis.
A.E.N.N. wrote the article.

Disclosure of interest

The authors declare that they have no competing interest.

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Original article

Characteristics of HPV infection in women at risk in Western Algeria

Caractéristiques de l'infection HPV chez des femmes à risque dans l'Ouest algérien

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Abstract

Objectives. – We aimed to characterize HPV infections and cervical lesions in Western Algeria.

Patients and methods. – A total of 96 cervical samples obtained from women at risk of HPV infection (HIV-1-infected or presenting with a gynecological disease) were analyzed to characterize this infection and search for cytological abnormalities.

Results. – A total of 60% of women at risk had an HPV infection. The rate of high-risk HPV (HR-HPV) infection among these women was 84.5% and that of intraepithelial lesions was 29.3%. The frequency of HPV infection was significantly higher among HIV-1-infected patients. An association between the presence of HR-HPV and the polygamy of the partner was observed. An association between cytological abnormalities and the use of oral contraceptives was observed among HIV-1-infected women.

Conclusion. – Given the high frequency of HPV infection in this at risk population, close monitoring and regular gynecological screening are essential.

Keywords: Algeria; HPV; HIV-1

Résumé

Objectif. – Cette étude a pour objectif de caractériser les infections à HPV et les lésions du col utérin dans l'Ouest algérien.

Patientes et méthodes. – Au total, 96 prélèvements cervicaux de femmes à risque d'infection HPV (séropositives au VIH-1 ou présentant une pathologie gynécologique) ont été testés pour la recherche de HPV et l'analyse cytologique.

Résultats. – Soixante pour cent des femmes présentaient une infection à HPV. Le taux de HPV à haut risque (HR-HPV) parmi les femmes infectées était de 84,5 % et celui des lésions intraépithéliales était de 29,3 %. La fréquence d'infection HPV était significativement plus élevée chez les patientes séropositives au VIH-1. Une association entre la présence de HR-HPV et la polygamie du partenaire était observée. Parmi les patientes séropositives pour le VIH-1, une association entre les anomalies cytologiques et l'utilisation de contraceptifs oraux a été observée.

Conclusion. – Le taux de HPV étant élevé dans cette population à risque, une surveillance gynécologique étroite et un dépistage régulier de ces patientes sont indispensables.

Mots clés : Algérie ; HPV ; VIH-1

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1. Introduction

Human papillomaviruses (HPV) are highly prevalent in the population. Approximately 80–90% of individuals are believed to have been infected by the virus during the course of their life [1].

These viruses with epithelial tropism are responsible for a wide variety of skin and mucosal lesions. There are approximately 100 characterized genotypes of the virus, but only 15 of them can lead to precancerous and cancerous lesions of the anal and genital mucous membranes. These genotypes are known as oncogenic or as high risk (HR) genotypes [2].

The persistent infection resulting from these HR-HPV genotypes is a necessary preliminary step towards cervical cancer [3]. HR-HPV genotypes are observed in more than 99% of cervical cancers [4,5]. This type of cancer is a real public health problem as it is the third most frequent cancer in women worldwide, and the first cause of female cancer in Africa [6].

The incidence of HPV infections, and especially of HR-HPV infections, is particularly high among HIV-1-infected women. Cervical cancer is the most frequent type of cancer in these women [7].

The prevention of cervical cancer relies on a conventional cytological screening as HPV tests and vaccines are not yet available in Algeria.

Very few studies focusing on cervical cancer and HPV infection have been conducted in Algeria [8,9], and the impact of a potential co-infection with HIV-1 has never been studied. We aimed to study HPV infections associated with cytological lesions observed in pap smears sampled from women at risk of infection, including HIV-1-infected women.

2. Patients and methods

We included 96 female patients considered at risk of HPV infection. A total of 64 women presenting with a gynecological disease were recruited at the private practices of Tlemcen, and 32 HIV-1-infected women were recruited at the reference center for STI/HIV/AIDS for Western Algeria.

Patients benefited from the following management:

- anamnesis to determine their social status and behavioral patterns;
- cervical and vaginal examination to look for cervical lesions;
- pap smear on a microscope slide for cytological examination;
- cervical sample on Preservcyt liquid medium (Hologic, Villepinte, France) for HPV detection and typing purposes.

Cytological results were interpreted on the basis of the Bethesda classification.

HPV detection and typing were performed using the DNA extracted from the Preservcyt medium samples. DNA extraction was performed using the automated extraction system NucliSENS easyMag® (Biomérieux, Craponne, France) with the extraction kit for nucleic acids. HPV detection and genotyping were performed using the INNO-LiPA HPV Genotyping Extra kit (Fujirebio, Courtaboeuf, France), according to previously described modalities [10,11]. This technique is able to identify 28 types of HPV, i.e. types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 69, 70, 71, 73, 74, and 82, including multiple HPV infections [10].

Data analysis was performed using the SPSS software. Chi^2 test and odds ratio with 95% CI were used to test the associations between various parameters.

Table 1
Social and demographic characteristics and behavioral patterns of patients infected with HPV in Western Algeria.
Caractéristiques sociodémographiques et habitudes comportementales de patientes infectées par le HPV dans l'Ouest Algérien.

Characteristics	
Mean age (min-max)	40.1 (23–72)
Mean age (min-max) of first sexual intercourse	20.3 (10–40)
Marital status (n = 58)	
Married	44 (75.9 %)
Divorced	5 (8.6 %)
Widow	6 (10.3 %)
Single	3 (5.2 %)
Number of sexual partners (n = 53)	
One	46 (86.8 %)
≥ 2 sexual partners	7 (13.2 %)
Polygamy of partner (n = 53)	
Yes	13 (24.5 %)
No	33 (62.3 %)
Unknown	7 (13.2 %)
Number of pregnancies (n = 58)	
0	3 (5.2 %)
1–3	29 (50 %)
> 3	26 (44.8 %)
Previous abortions (n = 58)	
Yes	20 (34.5 %)
No	38 (65.5 %)
Oral contraceptives (n = 58)	
Yes	33 (56.9 %)
No	25 (43.1 %)
Pap smear (n = 58)	
1st pap smear	49 (84.5 %)
Control pap smear	9 (15.5 %)
Clinical aspect of the cervix (n = 58)	
Normal	22 (37.9 %)
Abnormal	36 (62.1 %)
Smoking status (n = 58)	
Yes	2 (3.4 %)
No	56 (96.6 %)
HIV-1-infected (n = 58)	
No	34 (58.6 %)
Yes	24 (41.4 %)

3. Results

A HPV infection was observed in 60% (58/94) of patients. Social and demographic characteristics, as well as behavioral patterns, of the patients are detailed in Table 1. Mean age was 40.1 years and mean age of first sexual intercourse was 20.3 years. Most of these women were married and had only one sexual partner; they had had three pregnancies on average; never had an abortion performed; did not smoke; had no clinical cervical abnormality; had a pap smear performed for the very first time during the study; and used oral contraceptives.

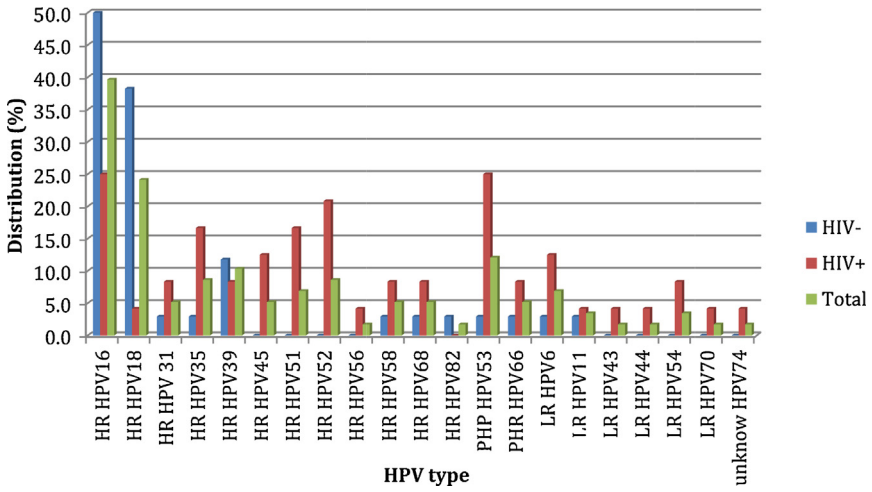

Fig. 1. Distribution of the various HPV genotypes in the study population.
Distribution des différents génotypes de HPV chez la population étudiée.

Table 2
HPV genotype distribution according to HIV-1 status.
Répartition des génotypes HPV selon le statut VIH-1.

HPV types	Total ($n=58$) (%)	HIV-1− ($n=34$) (%)	HIV-1+ ($n=24$) (%)	*P*	OR (95 % CI)
HPV 16	23 (39.7)	17 (50)	6 (25.0)	0.055	0.3 (0.1–1.1)
HPV 18	14 (24.1)	13 (38.2)	1 (4.2)	0.003	0.1 (0.01–0.5)
HR-HPV other than 16 and 18	27[a] (46.6)	10 (29.4)	17 (70.8)	0.002	5.8 (1.9–18.4)
pHR-HPV[b]	10 (17.2)	2 (5.9)	8 (33.3)	0.006	8 (1.5–42.1)
LR-HPV	11 (19)	3 (8.8)	8 (33.3)	0.019	5.2 (1.2–22.2)
Multiple HPV	22 (37.9)	8 (23.5)	14 (58.3)	0.007	4.6 (1.5–14.6)

[a] The total number is higher than the number of HR-HPV infections because of multiple HR-HPV infections.
[b] Genotypes 26, 53, and 66 were considered potentially high risk genotypes (pHR-HPV) according to Munoz et al. N Engl J Med 2003;348:518–27.

The results of the cytological examinations revealed abnormalities in 29.3% (17/58) of HPV infected women. Cytological abnormalities included: three (5.2%) atypical squamous cells of undetermined significance (ASC-US), 10 (17.2%) low-grade squamous intraepithelial lesions (LSIL), and four (6.9%) high-grade squamous intraepithelial lesions (HSIL).

As HR-HPV genotypes are observed in 84.5% (49/58) of HPV infections, HPV 16 and/or 18 are observed in 50% of infections. We identified 20 types of HPV, the most frequent being HPV 16 (39.7%), HPV 18 (24.1%), HPV 53 (12.1%), HPV 39 (10.3%), HPV 35 and HPV 52 (8.6%) (Fig. 1). Multiple HPV infections (two to four types) accounted for 37.9% (22/58) of HPV infections. At least one HR-HPV genotype was observed in 95.5% (21/22) of these multiple infections, with HPV 16 and/or 18 observed in 59.1% (13/22) of cases.

The HPV infection rate was significantly higher among women whose pap smears yielded cytological abnormalities than among women with a normal pap smear (83.3% vs 54.5%, OR = 4.2; CI: 1.12–15.57; $P = 0.025$).

The prevalence of HR-HPV and LR-HPV (low risk) infections was significantly higher among HIV-1-infected women. However, no significant difference was observed between the two groups for the prevalence of HPV 16 (Table 2). No significant difference was observed in terms of cytological abnormalities prevalence between HIV-1-infected women (6/24, 25%) and women non-infected with HIV-1 (10/34, 29.4%).

The rate of multiple HPV infections was 58.3% in HIV-1-infected women and 23.5% in women non-infected with HIV-1 (OR = 4.6; CI: 1.5–14.6; $P = 0.007$), with a higher number of HPV types (median = 3) in HIV-1-infected women than in women non-infected with HIV-1 (median = 2) ($P = 0.003$).

No relation between the development of high-grade lesions and the risk factors mentioned in the literature was observed in our study. However, we observed a relation between the presence of a HR-HPV infection and the polygamy of the partner ($P = 0.014$). We also observed an association among HIV-1-infected women between the presence of cytological abnormalities and the use of oral contraceptives ($P = 0.033$).

4. Discussion

To our knowledge, this is the first study focusing on HPV infections in Western Algeria and the first one to include HIV-1-infected patients in Algeria.

The HPV infection rate of approximately 85% that we observed in patients with abnormal pap smears is consistent with data obtained from meta-analyses [12].

HPV 16 and HPV 18 were the most frequent HR-HPV genotypes observed in our patients. They are also associated with the highest risk of progression to cervical cancer [1]. These genotypes are also targeted by the HPV vaccine and our results, although obtained with a small number of patients, suggest that vaccinating women in Algeria could have a real impact in terms of public health.

Consistent with data observed in the literature, we observed a higher prevalence of HR-HPV infections and of multiple HPV infections in HIV-1-infected women. This higher rate is mainly observed in HR-HPV infection caused by genotypes other than HPV 16 and 18, which is also consistent with previously published data [13–16].

We observed a significant association between HR-HPV infection and the polygamy of the partner. This has been defined as a risk factor in Algeria [8]; it highlights that the risk of developing cervical cancer for women is as much associated with their own sexual behavior as with that of their partner [17]. We also observed an association between cytological abnormalities and the use of oral contraceptives, especially among HIV-1-infected patients. Oral contraceptives are a well-known risk factor for cervical lesions [18].

Our study results thus highlight a high prevalence of HPV infections and cytological abnormalities of the cervix among women of Western Algeria who consulted for gynecological reasons or who were HIV-1-infected. Preventive measures should therefore be implemented in Algeria, such as HPV screening and vaccination.

Disclosure of interest

The authors declare that they have no competing interest.

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We would like to thank all individuals who contributed to the article: L. Boublenza wrote the study protocol and contributed to collecting samples. H. Hassaine supervised the study. J. Ngou contributed to the virological study. A. Nahet contributed to collecting samples and to the data analysis. M. Segondy supervised the virological study and contributed to writing the article. F. Razik performed the pap smears in HIV-infected patients. D. Regagba performed the statistical analysis. N. Sadouki and D. Mouhammedi contributed to writing the study protocol.

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Original article

Amoxicillin–clavulanic acid prescriptions at the Greater Paris University Hospitals (AP–HP)

Prescriptions d'amoxicilline–acide clavulanique à l'Assistance publique–Hôpitaux de Paris (AP–HP)

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Abstract

Objective. – We aimed to document amoxicillin–clavulanic acid prescription to improve the proper use of antibiotics in hospital settings. We used three criteria: quality of medical charts, adequacy of indications, and adequacy of treatment duration.

Method. – This study was designed as a one-day point prevalence survey carried out by antibiotic lead specialists.

Results. – We included 387 prescriptions from 32 hospitals. Immunodeficiency was recorded as a risk factor in 30% of patients. Computerized prescriptions were observed in 79% of cases. The indication was mentioned in 73% of cases and a 48/78-hour re-assessment of the antibiotic therapy was performed in 54% of cases. The antibiotic indication was primarily for pneumonia and was deemed appropriate in 75% of patients. Adult mean treatment duration was 11.1 days. Use of dual combination therapy and/or treatment duration exceeding two weeks accounted for the main reasons for an inappropriate use of antibiotics. Prescriptions recorded as having been made by senior physicians were of the shortest treatment duration ($P = 0.0163$).

Conclusion. – Medical charts should be better filled in. Reinforcing the role of senior physicians in supervising antibiotic prescriptions is likely to result in a better control of treatment duration and ultimately in a reduced antibiotic consumption. By reinforcing the collaboration between pharmacists and antibiotic lead specialists, the improvement of computerized prescriptions at hospital level should help better detect the "at risk" prescriptions, namely those exceeding seven days or those combining antibiotics.

Keywords: Amoxicillin–clavulanic acid; Antibiotic stewardship

Résumé

Objectif. – Améliorer le bon usage des antibiotiques à l'AP–HP en analysant la prescription d'amoxicilline–acide clavulanique à l'aide de trois critères : tenue du dossier médical, pertinence des indications et durée de traitement.

Méthode. – Enquête un jour donné menée par les référents antibiotiques.

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Résultats. – L'enquête a recensé 387 prescriptions dans 32 établissements. Un facteur de risque d'immunodépression était noté chez 30 % des patients. Les prescriptions étaient informatisées dans 79 % des cas. Le dossier mentionnait l'indication dans 73 % des cas et la réévaluation à 48/72 heures dans 54 % des cas. L'indication du traitement était majoritairement pour des infections pulmonaires. Elle a été jugée pertinente chez 75 % des patients. Chez l'adulte, la durée moyenne de traitement était de 11,1 jours. Le maximum de non-pertinence de l'indication et/ou de la posologie était noté chez les patients ayant des bithérapies et/ou des traitements de plus de deux semaines. La prescription dont la traçabilité mentionnait qu'elle émanait d'un senior était de durée plus courte ($p = 0{,}0163$).

Conclusion. – La tenue du dossier médical doit être améliorée. Un meilleur contrôle de la durée des prescriptions en renforçant le rôle des seniors dans le suivi des prescriptions devrait permettre de diminuer la consommation de cet antibiotique. Le bon niveau d'informatisation des prescriptions à l'AP–HP devrait permettre, en renforçant la connexion entre pharmaciens et référents antibiotiques, de mieux surveiller les prescriptions les plus à risque ; à savoir celles dépassant sept jours et celles associant plusieurs antibiotiques.

Mots clés : Amoxicilline–acide clavulanique ; Bon usage des antibiotiques

1. Introduction

The excessive use of antibiotics in France, in both community and hospital settings, led to the implementation of multiannual action plans [1]. The greater Paris university hospitals (French acronym AP–HP) includes all university hospitals of the Ile-de-France region, and is the largest hospital system in Europe. It includes 37 hospitals, grouped in 12 hospital groups. The hospitalization wards (> 24 hours) of the AP–HP had a total of 20,884 beds in 2014. The various wards include medicine, surgery, gynecology and obstetrics (MSO), pediatrics, and geriatrics, as well as downstream wards such as emergency departments and highly specialized units. The AP–HP activity accounts for a total of 1.2 million stays in MSO wards, i.e. 61% of the overall management for unscheduled stays in Ile-de-France and 53.9% of conventional hospitalization management in acute geriatrics wards [2].

The AP–HP has a central Anti-Infective Drug Committee (French acronym COMAI), but each hospital also has its own COMAI. They promote the proper use of antibiotics and draft recommendations. Every hospital has at least one antibiotic lead specialist, depending on the size of the hospital, as recommended by the national plan.

Antibiotic consumption in France increased by 4% between 2011 and 2012 while the number of hospital admission only raised by 1% [3]. This increase led the central hospital medical committees (French acronym CME) to issue a national warning and to implement a national plan. The authors of the national plan advocated for the need for bi-annual controls of antibiotic consumption and for the implementation of a survey assessing the consumption of a given antibiotic to analyze, raise awareness, and put forward a potential course of action.

They decided that the survey would assess the use of amoxicillin–clavulanic acid (AMOX–CLAV) as this antibiotic has been defined as a "critical antibiotic" by the French Agency for the Safety of Health Products (French acronym ANSM) as part of the national antibiotic plan [4]. AMOX–CLAV is also the most prescribed antibiotic at the AP–HP. The study was conducted by antibiotic lead specialists and had three objectives, as per the national antibiotic plan:

- to assess, in light of national recommendations, whether or not medical charts were properly filled in;
- to analyze the adequacy of prescriptions as per local recommendations;
- to assess treatment duration.

The study was also the opportunity to assess the antibiotic lead specialists' reactivity and networking activities within the AP–HP.

2. Patients and methods

The study was coordinated by the pharmaceutical assessment and stewardship unit of the AP–HP General Agency for Equipment and Health Products (French acronym AGEPS), which acts as the scientific administration office of the AP–HP COMAI. Every hospital of the AP–HP was invited to take part in the study. The study was designed as a one-day point prevalence survey and focused on medical and surgical activities over 24 hours, including pediatrics and geriatrics. Rehabilitation and long-term care wards were also included. All activities related to day hospitalization and operating rooms were excluded, just like all antibiotic prophylaxis-related activities.

The study took place between April 15 and May 15, 2014 to avoid the excessive antibiotic consumption observed during winter. The study was conducted by antibiotic lead specialists. The lead specialists asked the ward's executive the name of patients who had received the studied antibiotic on the day of the survey so as to ensure study comprehensiveness. Patients exposed to the studied antibiotic were defined as having received the antibiotic following prescription implemented from 9am onwards.

The study consisted in reviewing the patient's medical chart using a predefined questionnaire. Lead specialists were asked not to discuss the charts with prescribers. Answers to the predefined questionnaire were then fed into a computerized form, and it was kept for 14 days so that the date of treatment cessation could then be reported onto it. A closed questionnaire was chosen to facilitate the analysis. The questionnaire is described in Appendix 1.

The questionnaire consisted of several sections:

- the first part focused on background data: specialty of the ward, number of patients hospitalized in the ward on the day of the survey, demographic data, date/dose/route of administration of the first dose of AMOX–CLAV received, and whether the antibiotic was administered as a monotherapy or as a combination therapy;
- the second section focused on the prescription and on information written in the medical charts: computerized prescription, mention of the initial indication or lack of it, prescriber's signature traceability (junior or senior physician), treatment switch from a previous antibiotic therapy or transferred from another ward, and mention of the date of treatment discontinuation or lack of it. We took into consideration any re-evaluation of the prescription after 48/72 hours to assess the adequacy of the prescription. We did not take into consideration the re-evaluation on Day 7 as treatment duration with the studied antibiotic is usually short. We took note of the route of administration;
- the third section focused on the indication: based on what had been written on the patient's chart;
- the fourth section focused on microbiological data: we aimed to assess if the prescription had been guided by the results of a microbiological examination;
- antibiotic lead specialists were asked to assess the prescription adequacy at the time of indication according to the hospital's recommendations:
  - adequacy of the indication: three possible choices (appropriate, inappropriate, and could have been further discussed) on the basis of local recommendations on the proper use of the studied antibiotic, if available, or of pulmonary infection, skin infection, and urinary tract infection recommendations,
  - adequacy of the prescribed dose: two possible choices (appropriate or inappropriate) on the basis of the marketing authorization,
  - adequacy of the combination prescribed: three possible choices (appropriate, could have been further discussed, inappropriate),
  - two questions were then asked to the antibiotic lead specialist: Do you think that the antibiotic prescription was unnecessary? Do you think that another antibiotic therapy should have been considered?;
- the final section of the survey focused on the date of treatment discontinuation, considering the evaluation on Day 14. If the patient was still receiving the studied antibiotic, the scheduled date of discontinuation had to be written down, irrespective of the patient still being hospitalized or having been discharged.

The computerized data collection form was designed with a free open source module on the joomla platform. It was then uploaded on the Intranet of all hospitals. Collected data was fed into the software by the antibiotic lead specialist or by the hospital pharmacist.

Statistical analyses were performed using the R®3.1.2 software. Univariate analyses were performed using Student's t-test for quantitative variables and Chi-square test for qualitative variables. Linear regression models were performed to look for correlations between variables.

3. Results

A total of 32 hospitals (86%) took part in the study. The assessed prescriptions had been made to 387 patients (360 adults and 27 children) hospitalized in the surgical ward (25%), medical ward (43%), ICU (8%), pediatrics ward (8%), rehabilitation ward (6%), long-term care unit (12%), and short-term care unit (< 1%). Mean age of patients was 68 years [0.3–102] and mean weight was 66.7 kg [4–155]. A risk factor such as cancer, immunodeficiency, or transplant was observed in 30% of patients.

Information written in the medical charts is described in Table 1. Treatment indication was mentioned in 73% of the charts, but in only 48% of surgical charts. The initial prescription had been written by a junior physician in 56% of cases and by a senior physician in 44% of adult case patients. Prescription re-evaluation at 48/72 hours was mentioned for 54% of patients. The scheduled date of treatment discontinuation was mentioned for 63% of patients. Mean and median treatment duration were 10.2 days and 8 days, respectively. Overall, 79% of prescriptions were computerized. The Phedra® software was most often used (45%), followed by Actipidos® (39%). An oral treatment was administered to 61% of patients. The median daily dose prescribed was 3 g/day [1–12] for adults. A total of 30 patients received a higher daily dose.

An empirical treatment was prescribed to 82% of patients. Among them, 81% were prescribed a monotherapy and 71% received a first-line antibiotic therapy. Treatment was initiated in another ward for 79 patients. Overall, 9% of prescriptions followed another prescription made in the emergency ward.

Fig. 1 details the indications for AMOX–CLAV prescription. Most prescriptions were made for pulmonary infections (45%): aspiration pneumonia (29%), bronchodilation or COPD decompensation (26%), infections in patients presenting with a chronic respiratory failure (14%), and pulmonary abscess (4%). Pneumonia accounted for 16% of pulmonary infections.

A bacteriological documentation was observed in 28% of cases (111 charts). The four bacteria and/or species most often isolated were *Escherichia coli* (28%), *Streptococcus aureus* (18%), *Streptococcus* (15%), and other Enterobacteriaceae (14%). In 59% of medical charts ($n = 66/111$ charts), a note indicated that treatment was initiated following the identification of the bacterium, and mentioned that the isolated bacterium was susceptible to AMOX–CLAV in 86% of cases.

Table 2 details the adequacy of the prescriptions as well as treatment duration. Prescriptions were deemed appropriate for 75% of patients, inappropriate for 14%, and the antibiotic lead specialist thought that it could have been further discussed for 11% of patients. The antibiotic lead specialist thought that the choice of AMOX–CLAV was inappropriate for 51 patients (13%). Doses were deemed appropriate for all children and for 93% of adults. Doses administered to the 30 patients receiving more than 3 g/day were deemed appropriate for 28 of them and the indication was considered appropriate for 26 of them.

Table 1
Quality of medical chart.
Tenue du dossier.

	Adult patients ($n=360$)										Pediatric patients ($n=27$)	
	Total ($n=360$)		Medicine ($n=169$)		Surgery ($n=95$)		ICU ($n=26$)		Rehabilitation and long-term care wards ($n=63$)			
Prescriber												
Junior physician	200	56%	112	66%	54	57%	11	42%	18	29%	13	48%
Senior physician	160	44%	57	34%	41	43%	15	58%	45	71%	14	52%
Indication written in the chart												
Yes	262	73%	138	82%	46	48%	23	88%	50	79%	25	93%
No	93	26%	31	18%	46	48%	2	8%	12	19%	2	7%
Unknown	5	1%	–	–	3	3%	1	4%	1	2%	–	–
Re-evaluation at 48/72 hours mentioned in the chart												
Yes	193	54%	96	57%	44	46%	19	73%	29	46%	7	26%
No	142	39%	63	37%	44	46%	4	15%	29	46%	19	70%
Unknown	25	7%	10	6%	7	7%	3	12%	5	8%	1	4%
Scheduled treatment duration												
Scheduled date of treatment discontinuation	226	63%	105	62%	36	38%	12	46%	56	89%	19	76%

A total of 63 patients received AMOX–CLAV in combination with another antibiotic; this prescription was considered inappropriate in 43% of cases.

Treatment duration was defined for 342 patients (88%): 315 adults and 27 children. Table 2 details treatment duration. Mean treatment duration was 11.1 days (1 to 79 days) in adults and median treatment duration was 8 days (Q1–Q3 6–12 days). Table 3 details treatment duration by indications.

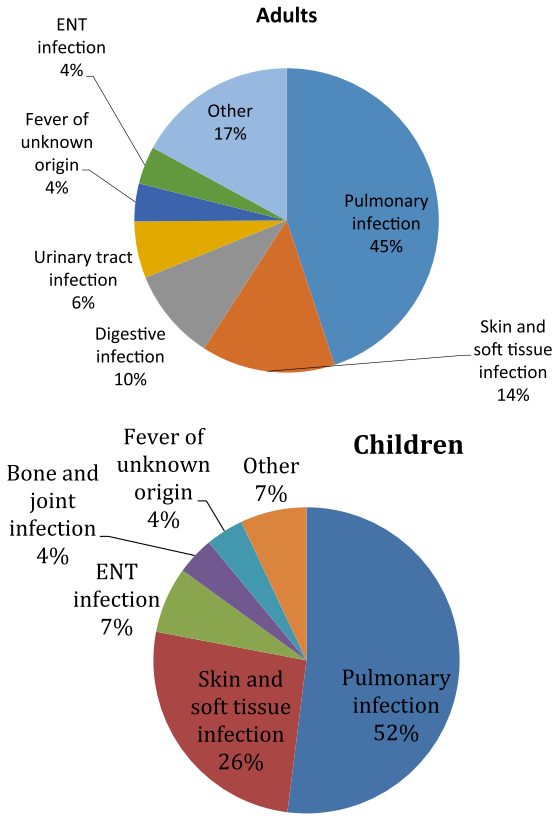

Fig. 1. Treatment indications.
Indications des traitements.

Treatment duration in adults was significantly correlated with the prescriber's status, i.e. if the prescriber was a senior physician treatment duration was shorter ($P=0.0163$). However, we did not observe any correlation between treatment duration and the mention of a re-evaluation in the chart (only mentioned in 55% of the charts). We observed a significant correlation ($P=0.005$) between inappropriate doses and excessive treatment duration.

Out of the 46 prescriptions made for more than 15 days, the antibiotic lead specialist thought that the antibiotic prescription was useless in six cases, that another antibiotic should have been prescribed in nine cases, that the doses prescribed were inappropriate in eight cases, and that the combinations were inappropriate in 17 cases.

4. Discussion

The study was conducted during spring to avoid the impact of winter infections, and we believe it to be representative of the population of patients managed at the AP–HP. We registered 387 patients exposed to AMOX–CLAV in 32 hospitals. This figure is consistent with the results of the 2012 study of healthcare-associated infection prevalence [5] (491 prescriptions in 38 hospitals). Computerized prescriptions were observed in 79% of cases. As part of the 2013 antibiotic stewardship, 67% of beds at the AP–HP benefited from a computerized management. This figure confirms the growing computerization of prescriptions.

Treatment indication was registered in the medical charts in only 74% of cases and in only 48% of cases for surgical patients. The figure for the 48/72-hour re-evaluation is also far from being optimal as the re-evaluation is only mentioned in 55% of the charts. The lack of mention of the prescription indication or re-evaluation in the charts does not necessarily imply that the medical team did not discuss the case. These criteria are

Table 2
Treatment duration and adequacy of indications.
Durée de traitement et évaluation de la pertinence du traitement.

	Adult patients ($n = 360$)										Pediatric patients ($n = 27$)	
	Total ($n = 360$)		Medicine ($n = 169$)		Surgery ($n = 95$)		ICU ($n = 26$)		Rehabilitation and long-term care wards ($n = 63$)			
	n	Days	*n*	Days	*n*	Days	*n*	Days	*n*	Days	*n*	Days
Treatment duration												
Median		8		8		7		6		7		9
Q1–Q3		6–12		7–13		5–13		5–8		6–10		5–10
Mean	315	11.1	149	10.7	73	10.5	25	7.3	61	10	27	8.8
Standard deviation		10.6		9.2		9.2		6.4		8.7		4.2
Min–Max		1–79		1–68		1–42		2–34		1–40		2–18

	Evaluation by the antibiotic lead specialist											
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Adequacy of the indication												
Appropriate	260	73	126	75	58	61	26	100	44	70	22	81
Inappropriate	52	14	26	15	15	16	–	–	11	17	2	7
Could have been further discussed	44	11	14	8	19	20	–	–	7	11	3	11
Unknown	7	2	3	2	3	3	–	–	1	2	–	–
Adequacy of treatment modalities												
Appropriate	323	90	154	91	85	89	25	96	54	86	25	93
Inappropriate	26	7	11	7	8	8	–	–	5	8	2	7
Unknown	11	3	4	2	2	2	1	4	4	6	–	–
Adequacy of the combination therapy												
Inappropriate	24	42	11	50	7	37	4	66	2	25	3	50
Appropriate	21	37	7	32	10	53	1	17	1	13	2	33
Could have been further discussed	5	12	2	9	1	5	1	17	2	25	1	17
Unknown	8	9	2	9	1	5	–	–	3	37	–	–
Total number of combined therapies	58	100	22	100	19	100	6	100	8	100	6	100
Should the antibiotic prescription have been avoided?												
Yes	48	13	20	12	16	17	1	4	10	16	3	11
No	301	84	146	86	75	79	25	96	49	78	24	89
Unknown	11	3	3	2	4	4	–	–	8	13	–	–
Should another antibiotic therapy have been considered?												
Yes	59	16	23	12	24	25	2	8	7	77	5	19
No	279	78	139	86	64	67	24	92	48	11	20	74
Unknown	22	6	7	2	7	7	–	–	8	13	2	7
As for the isolated bacterium, was there any other antibiotic with a narrower spectrum of activity (amoxicillin)?												
Yes	32	31	14	38	9	26	2	11	2	22	4	44
No	61	62	19	51	25	71	16	89	6	67	5	56
Unknown	6	7	4	11	1	3	–	–	1	11	–	–
Total number of microbiological examinations	99	100	37	100	35	100	18	100	9	100	9	100

mentioned in the national plan and aim at improving the quality of patient management; they are therefore associated with a greater strictness.

As expected, the main indication for AMOX–CLAV was pulmonary infections and most prescriptions were empirical. Prescribing AMOX–CLAV for pulmonary infections is consistent with the recommendations. Pneumonia, which should be treated with amoxicillin alone, accounted for only 16% of pulmonary indications observed in our study.

The indication was deemed appropriate in 75% of cases. This figure is relatively high compared with the various studies aiming at evaluating the adequacy of antibiotic therapies in hospital settings [6–9]; the proportion of appropriate prescriptions in those studies is rather around 60%. We observed a similar percentage (60%) for surgical prescriptions. One needs to be very cautious when retrospectively assessing the adequacy of a prescription, especially when evaluating empirical treatment prescriptions such as the ones made for pulmonary infections. Our prevalence of antibiotic therapies deemed useless was lower than the one observed in other studies [10,11]. Comparing the rates of antibiotic prescription adequacy observed in the literature is difficult because of several factors: monocentric or multicenter nature of the studies, evaluation during a given infection such as pulmonary or urinary tract infections. We thought that AMOX–CLAV would be mostly prescribed as an empirical treatment, making the use of microbiological data

Table 3
Treatment duration according to the five main indications.
Durées des traitements en fonction des cinq principales indications.

	All prescriptions ($n = 387$)		Adult prescriptions ($n = 360$)		Pediatric prescriptions ($n = 27$)	
	n	Days	*n*	Days	*n*	Days
Pulmonary infection						
Median		8		7		9
Q1–Q3		6–10		6–10		7–10
Mean	166	10.7	152	10.9	14	8.6
Min–Max		0–73		0–73		4–15
Skin and soft tissue infection						
Median		10		11		10
Q1–Q3		6–15		6–15		3–10
Mean	61	12.3	54	12.9	7	7.9
Min–Max		0–47		0–47		2–15
Digestive infection						
Median		7		7		
Q1–Q3		4–10		4–10		
Mean	29	8.4	29	8.4		
Min–Max		1–38		1–38		
Urinary tract infection						
Median		7		7		
Q1–Q3		5–10.5		5–10.5		
Mean	24	8.2	24	8.2		
Min–Max		2–20		2–20		
Fever of unknown origin						
Median		7		7		1
Q1–Q3		4–11		4–11		10–10
Mean	14	8.6	13	8.5	1	10
Min–Max		1–27		1–27		10–10

less useful to assess the adequacy of the prescription. Antibiotic misuse is difficult to assess. This is why we asked lead specialists two questions in order to assess it: Is the antibiotic therapy prescribed appropriate? Do you think this antibiotic should not have been prescribed? Both percentages obtained from these answers are consistent with each other. The combined treatment was often deemed inappropriate when AMOX–CLAV was combined with other antibiotics (43% of cases). The prescription of a dual combination therapy should therefore be used as a warning sign in the fight against antibiotic misuse [11].

The median exposure to AMOX–CLAV in adults and children was eight days (10.9 days on average). This figure was quite similar across the various wards (medicine, surgery, pediatrics, rehabilitation/long-term care wards). The mean exposure for pulmonary infections was 10.7 days, which is consistent with the 2006 consensus conference [12]. When treatment duration was longer than 15 days, the number of inappropriate prescriptions increased in terms of indication, doses, or prescribed combinations. All prescriptions made for more than seven days should therefore be justified, just like it is required by the ICATB2 score [1].

Our study results indicate that prescriptions made by senior physicians were always of a shorter duration than the ones made by junior physicians. This is quite comforting, especially as very few studies have taken this criterion into consideration. However, Demonchy et al. [12] did not observe such difference. They assessed this criterion in the emergency department only, where most prescribers are junior physicians. It is quite normal to think that the younger a physician is, the longer his prescription will be to reassure himself. Antibiotic therapy prescription is also suffering from too many imprecisions: the marketing authorizations are often dated and have never been updated, and consensus conferences indicate ranges of duration that justify any longer treatment duration prescribed by younger physicians. Better defining minimum antibiotic therapy duration is one of the priorities identified by the Infectious Disease Society of America (IDSA) [13]. Thus, the 2006 French consensus conference [14] recommends treatment duration ranging from 7 to 14 days for pneumonia, while the American society for pulmonology recommends 7 to 10 days [15] and the American society for infectious diseases recommends to discontinue the antibiotic therapy 72 hours after apyrexia [16]. We understand that the implementation of such recommendations requires experience.

As France is the fourth largest consumer of antibiotics in Europe, this excessive use must be reduced [17]. The relation between this excessive consumption and the emergence of resistance cannot be questioned any longer [18]. It is well known that reducing antibiotic exposure through better indications and shorter treatment duration can lead to reducing the selection pressure on bacteria of the endogenous flora [19–22]. The overall antibiotic consumption at the AP–HP reached 520 DDD/1000 hospital day in 2012. This figure is slightly lower (by 32 DDD) to the antibiotic consumption figure of all university hospitals of France [23]. AMOX–CLAV consumption was 140 DDD/1000 hospital day, which is slightly higher than the figure observed

in other university hospitals (by 7 DDD) but lower than that observed in non-university hospitals (by 14 DDD). This difference between university and non-university hospitals highlights the difficult comparison of antibiotic consumption between healthcare facilities. Antibiotic consumption at the AP–HP varies by sites [3], mainly because of the activities performed in each hospital.

Our study, which was the first cross-sectional study conducted at the AP–HP to assess the adequacy and duration of antibiotic prescriptions, has several biases but gives the opportunity to describe the use of AMOX–CLAV using antibiotic lead specialists as evaluators. A dual evaluation of antibiotic prescription adequacy would have been ideal, using advanced algorithms, but the current means do not allow for performing such an evaluation. Nevertheless, the study puts forward several suggestions to better use antibiotics at the AP–HP. We demonstrated that the AP–HP could rely on a strong network of antibiotic lead specialists, even though their modus operandi varies by facility. Their busy schedule prevents them from assessing all antibiotic prescriptions; for instance, they do not have time to assess the prescriptions of penems. The antibiotic lead specialists' ability to critically assess a prescription suggests that they should be further involved in the larger prescription assessment. The 2011–2016 national plan is asking for a consolidation and extension of the antibiotic lead specialist roles. The time dedicated to that activity should thus be better defined at the AP–HP. An interesting option lies in strengthening the role of senior physicians in the control of prescription adequacy and duration. Shorter prescriptions will certainly lead to savings as they would be associated with fewer adverse effects [24] and with shorter hospital stays [25,26]. Treatments lasting less than seven days have already proved appropriate in the treatment of pneumonia [27–30]. Implementing warning systems involving pharmacists and lead specialists, through the use of adapted computerized tools, should help in raising awareness of senior physicians on prolonged prescriptions or on useless antibiotic combinations. Our study confirmed that developing and improving the computerized management of patients should help in implementing these warning systems.

5. Conclusion

Patient charts must be better filled in. Improving the control of antibiotic prescription duration by strengthening the role of senior physicians should help in reducing the consumption of AMOX–CLAV. The good computerized prescription system available at the AP–HP should help in better monitoring high-risk prescriptions (>7 days and antibiotic combinations) by strengthening the collaboration between pharmacists and antibiotic lead specialists.

Contributors

Isabelle Fusier contributed to designing the study, implementing the study, performing the statistical analysis, interpreting the results, and writing the article.

Olivier Parent de Curzon contributed to implementing the software for data collection, building the database, and performing the statistical analysis.

Sophie Touratier, Leila Escaut, and Matthieu contributed to designing the study, performing the study in their hospital, and reviewing the article.

Sandra Fournier, Martine Sinègre, and Philippe Lechat contributed to designing the study and reviewing the article.

Daniel Vittecoq was the study instigator, contributed to designing the study, performing the study in his hospital, interpreting the results, and writing the article.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medmal.2016.09.003.

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Original article

Transversal infectious disease activity in French hospitals☆

L'infectiologie transversale dans les hôpitaux français

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Abstract

Objectives. – To assess the organization, activity, and funding of transversal infectious diseases (ID) activity in French hospitals.

Methods. – Cross-sectional questionnaire-based survey conducted in 2013–2014.

Results. – The questionnaire was returned by 66 hospitals (response rate: 63%). A transversal ID consultancy activity was present in 65 hospitals (98%) and had existed for a median of 6 years. The median team size for transversal ID activity was equivalent to 0.8 full-time physicians. Among the 16 hospitals (25%) with a full-time physician dedicated to transversal ID activity, only 6 university hospitals received dedicated funding. Teams with a transversal ID activity received a median of 35 calls for advice (IQR = 20–60) per week from other hospital departments, and 14 calls from external structures. They participated in multidisciplinary meetings (75%), dedicated staff meetings (bacteriologists, pharmacists, or infection control physicians – 51%), and promoted antibiotic stewardship (antibiotic usage guidelines (72%) and auditing (62%)). Eleven teams (17%) prepared an annual report of their transversal ID activity, and 30 teams (46%) recorded the number of calls for advice. Twenty-one teams cross-charged their in-hospital transversal ID consultancy, and 5 teams invoiced their external consultancy, with a recovery of the relevant funds by 8 teams.

Conclusion. – Although most French hospitals that responded to this survey had a transversal ID consultancy activity, not all had implemented an antibiotic stewardship program. Few teams conducted standardized data collection or cross-charged their transversal ID activity. Moreover, teams rarely received specific funding for a full-time ID physician dedicated to transversal ID activity.

Keywords: Infectious diseases; In-hospital consultancy; Antibiotic stewardship

Résumé

Objectif. – Analyser l'organisation, les pratiques et le financement de l'infectiologie transversale dans les hôpitaux français.

Méthodes. – Étude transversale sur questionnaire (2013–2014).

Résultats. – Soixante-six hôpitaux ont retourné le questionnaire (taux de réponse : 63 %). Une consultation d'infectiologie transversale était présente dans 65 hôpitaux (98 %) depuis 6 ans (IQR = 4–10), et 0,8 médecins équivalent temps-plein exerçaient une activité d'infectiologie

☆ Part of this data was presented as an oral communication at the 35th RICAI in Paris, December 2015.

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transversale. Parmi les 16 hôpitaux (25 %) ayant un médecin temps-plein pour l'activité d'infectiologie transversale, seulement 6 hôpitaux universitaires avaient un financement spécifique. Les équipes ayant une activité d'infectiologie transversale recevaient 35 appels téléphoniques (IQR = 20–60) par semaine des autres services et 14 appels de l'extérieur. Elles participaient à des réunions de concertation pluridisciplinaires (75 %), à des réunions dédiées avec les bactériologistes, pharmaciens ou hygiénistes (51 %) et à la politique d'utilisation des antibiotiques (recommandations sur l'antibiothérapie [72 %], audits [62 %]). Onze équipes (17 %) rédigeaient un rapport annuel sur leur activité d'infectiologie transversale et 30 (46 %) comptabilisaient le nombre d'avis téléphoniques. L'activité d'infectiologie transversale intrahospitalière était financièrement valorisée par 21 équipes et l'activité extrahospitalière par 5, avec un reversement de cette valorisation financière à 8 équipes. **Conclusion**

Bien que la plupart des hôpitaux aient organisé des consultations d'infectiologie transversale, tous n'avaient pas finalisé un programme de bon usage des antibiotiques. Peu d'hôpitaux avaient mis en place un recueil standardisé de leur activité d'infectiologie transversale ou la valorisaient financièrement. De plus, peu d'équipes recevaient un financement spécifique pour des postes médicaux dédiés à cette activité.

Mots clés : Maladies infectieuses ; Consultation intrahospitalière ; Bon usage des antibiotiques

1. Introduction

With the increase in antimicrobial resistance and in the number of patients presenting with immunodeficiencies and/or complex infections, infectious disease (ID) experts are increasingly required to provide advice on ID diagnosis and treatment of hospitalized patients [1]. The implementation of a national policy on antibiotic usage has contributed to the creation of transversal ID teams in French hospitals over the last decade [2].

ID specialists are increasingly engaging in transversal activity with other hospital wards and in antibiotic stewardship programs indirectly linked to patient care, such as the development of practice guidelines, performance indicators (with the implementation of improvement measures), teaching, and research [3,4].

By ensuring more appropriate antimicrobial therapies, transversal ID teams improve patient diagnoses and outcomes, avoid adverse drug reactions, shorten the hospital stay, and reduce antibiotic consumption [5–8]. It has been shown that ID specialist interventions have a positive impact on patient management, care quality, and hospitalization costs [8–10].

In France, few transversal ID teams are properly funded. Indeed, the French system of resource allocation for public hospitals [11] is poorly adapted to transversal activities: reimbursement for hospitalization is based on a pricing list in which each disease, and its severity, is associated with a fixed cost. Time devoted to transversal ID activity is rarely taken into account.

To obtain a picture of transversal ID activity and its funding in French hospitals, the National Union of Infectious Disease Specialists (French acronym SNMinf) conducted a national cross-sectional survey in 2013–2014 among ID physicians. The aim was to describe the organization, activity, and funding of transversal ID activity in French hospitals in order to help harmonize transversal ID practices and to promote their funding.

2. Methods

2.1. Study design

This national cross-sectional survey of transversal ID activity was based on a standardized self-administered questionnaire. The questionnaire, along with a covering letter, was sent by mail or by e-mail in 2013, followed by a reminder in 2014.

2.2. Study population

The questionnaire was circulated to 104 physicians listed as ID specialists by the French Infectious Diseases Society (French acronym SPILF) or the SNMinf, and working in French university, general, military, or private hospitals. If several ID physicians were listed as working in the same hospital, only the most highly qualified physician received the questionnaire. Thus, only one questionnaire was sent per hospital.

2.3. Questionnaire

The questionnaire was divided into two sections, one focusing on the organization of transversal ID consultancy activity and antimicrobial stewardship, and the other on the funding of these activities.

The organizational questions concerned the staff (number of physicians and grade), the premises (dedicated office and phone line), the number of calls received per week from other wards of the same hospital and from external structures, the wards seeking advice, data recording, and interdisciplinary collaboration. Other questions focused on antibiotic stewardship. The questions concerning the funding of these activities included cross-charging (as a patient consultation for example), and repayment of the relevant sums to the teams.

2.4. Statistical analysis

Data was analyzed with SPSS software for Windows™ version 17.0. Categorical variables were described by their frequencies and 95% confidence intervals, based on the normal approximation for binomial proportions, and continuous variables by their median and interquartile range (IQR), reported as lower and upper quartiles. To test for differences between university and non-university hospitals (i.e. general, private, or military hospitals), we used the chi-square test or Fisher's exact test for categorical data and the Wilcoxon Mann-Whitney test for continuous data. Statistical significance was set at 0.05.

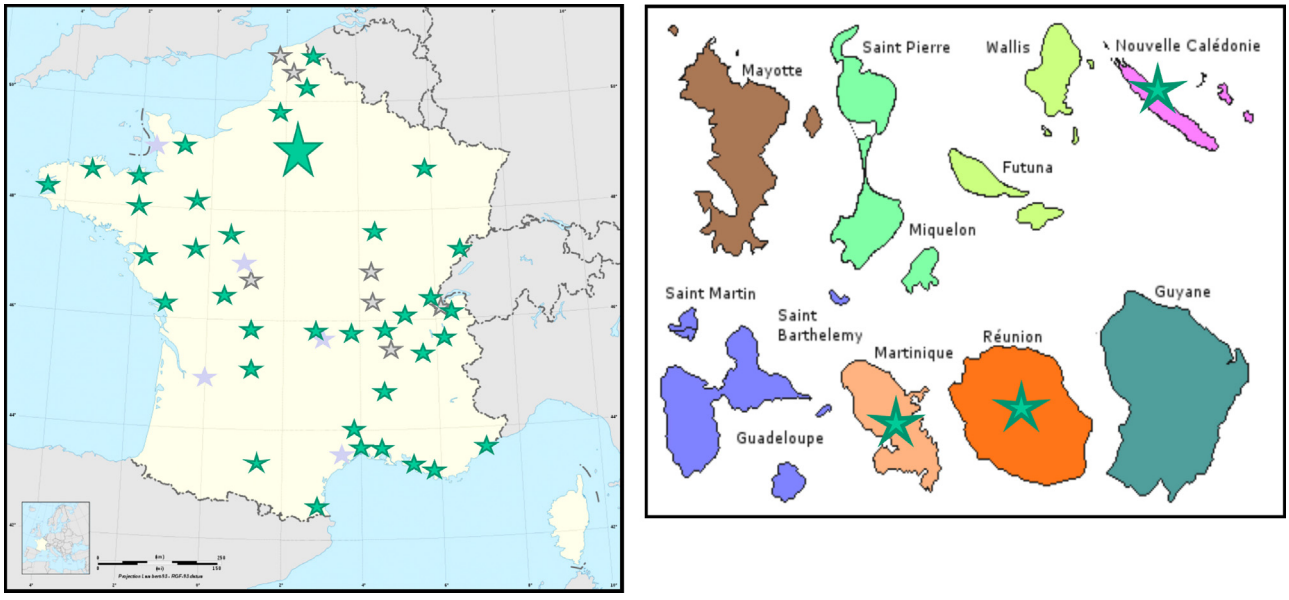

Figure 1. Geographic distribution of teams with transversal ID activity who responded to the questionnaire.
Répartition géographique des équipes médicales avec une activité d'infectiologie transversale ayant répondu au questionnaire.

3. Results

3.1. Characteristics of responding teams

Sixty-six (63%) of the 104 solicited teams returned the completed questionnaire. The 66 responding teams belonged to university (49%), general (44%), private (4%), or military hospitals (3%). Their geographic distribution is shown in Fig. 1, and their home hospitals are listed in the acknowledgements. There was no difference ($P = 0.185$) between responding teams and non-responding teams with respect to their distribution among university, general, military, and private hospitals. Among the 66 responding teams, 35 (53%) were located in an ID specialist ward, 22 (33%) in a mixed ward (usually ID plus internal medicine), and 9 (14%) in wards not specifically devoted to IDs. Only one team reported no formal transversal ID consultancy activity. The remaining 65 respondents reported that the transversal ID consultancy activity had been in place for a median of 6 years overall (IQR = 4–10): 10 years (IQR = 5–15) in university hospitals and 5 years (IQR = 3–7) in non-university hospitals ($P = 0.001$).

3.2. Types of transversal ID activities carried out by the responding teams

The main transversal ID activity of the teams consisted in providing advice to other wards, with a median of 35 requests per week. Six teams received 100 or more requests per week (Table 1). The requests mainly came from medical (48%) and surgical (31%) wards, as shown in Fig. 2. Only 34% of the teams wrote notes for patient records after a request. Fifty teams (76%) also received calls from external medical structures (median of 14 requests per week).

Three-quarters of the teams participated in multidisciplinary meetings with various hospital departments (mainly orthopedic wards, $n = 41$), at least once a week in two-thirds of cases. Half the teams participated in regular working groups with bacteriologists, pharmacists, or infection control physicians, and 40% reported the results of positive blood culture directly to the wards concerned.

The teams also participated in antibiotic stewardship, preparing antibiotic usage guidelines (72%), conducting audits (62%), and engaging in other activities such as education, commissions, and scientific studies (35%).

3.3. Staffing and resources for transversal ID activity

The median number of physicians dedicated to transversal ID activity in the responding hospitals was 0.8 full-time equivalents overall, 1.0 in university hospitals, and 0.5 in non-university hospitals (Table 2). The biggest hospitals had the highest staffing level dedicated to transversal ID activity: 1.0 physician in hospitals with 700 or more acute beds (1.1 in university hospitals and 0.9 in non-university hospitals) and 0.5 in hospitals (university and non-university) with fewer than 700 acute beds.

Among the 16 hospitals (25%) with a dedicated full-time ID physician, six (exclusively university hospitals) provided specific funding for a physician dedicated to transversal ID activity. A permanent transversal ID consultancy service was available in 34 hospitals (52%), and operated 24/7 in 55% of cases. In 72% of cases, the transversal ID activity was shared among bacteriologists (62%), pharmacists (49%), and infection control physicians (46%), each working in this role for a median of 2 hours (IQR = 1–4) per week.

A dedicated phone line or pager for transversal ID activity was available for 50 teams (77%), and dedicated premises were set aside for 10 teams (16%). Dedicated funding for these premises was provided in only 4 cases (40%).

Table 1
Types of transversal ID activity carried out by the teams in France in 2013.
Description des activités réalisées par les équipes médicales ayant une activité d'infectiologie transversale en France en 2013.

	All hospitals			University hospitals			Non-university hospitals			
	n/*N*	% or median	95% CI or IQR	*n*/*N*	% or median	95% CI or IQR	*n*/*N*	% or median	95% CI or IQR	*P*
Advice on individual inpatients										
Inpatient consultations	65/66	98%	92–100	31/32	97%	84–100	34/34	100%	90–100	0.485
Median weekly number of calls from other hospital wards		35	20–60		55	30–95		20	13–44	<0.001
Median weekly number of calls from external structures		14	7–25		20	10–50		10	4–20	0.022
Percentage of teams writing notes for patient records	22/65	34%	23–47	9/31	29%	14–48	13/34	38%	22–56	0.434
Direct reporting to hospital wards of the results of a positive blood culture	26/65	40%	28–53	12/31	39%	22–58	14/34	41%	27–59	0.839
Participation in multidisciplinary meetings in hospital wards	49/65	75%	63–85	27/31	87%	70–96	22/34	65%	46–80	0.036
Once a week or more often	26/41	63%	47–78	18/23	78%	56–93	8/18	44%	22–69	0.026
Once a month	10/41	24%	12–40	3/23	13%	3–34	7/18	39%	17–64	0.153
Dedicated staff with bacteriologists, pharmacists, or infection control physicians	33/65	51%	38–63	16/31	52%	33–70	17/34	50%	32–68	0.897
Antibiotic stewardship										
Writing of antibiotic guidelines	47/65	72%	60–83	23/31	74%	55–88	24/34	71%	53–85	0.746
Auditing	40/65	62%	49–73	19/31	61%	42–78	21/34	62%	44–78	0.969
Auditing or writing of antibiotic guidelines	50/65	77%	65–86	25/31	81%	63–93	25/34	74%	56–87	0.496
Other activities (training, commissions, studies, etc.)	23/65	35%	24–48	13/31	42%	25–61	10/34	29%	15–47	0.292

3.4. Recording, funding, and charging of transversal ID activity

The number of calls for advice received from hospital wards was systematically recorded by 30 teams (46%), and regular reports on this activity were prepared by 40 teams (62%). Among the 50 teams that received calls from external structures, 13 (26%) prepared an annual report on this activity. An annual report on overall transversal ID activity was prepared by only 11 teams (17%); 8 in university hospitals and 3 in non-university hospitals ($P = 0.068$).

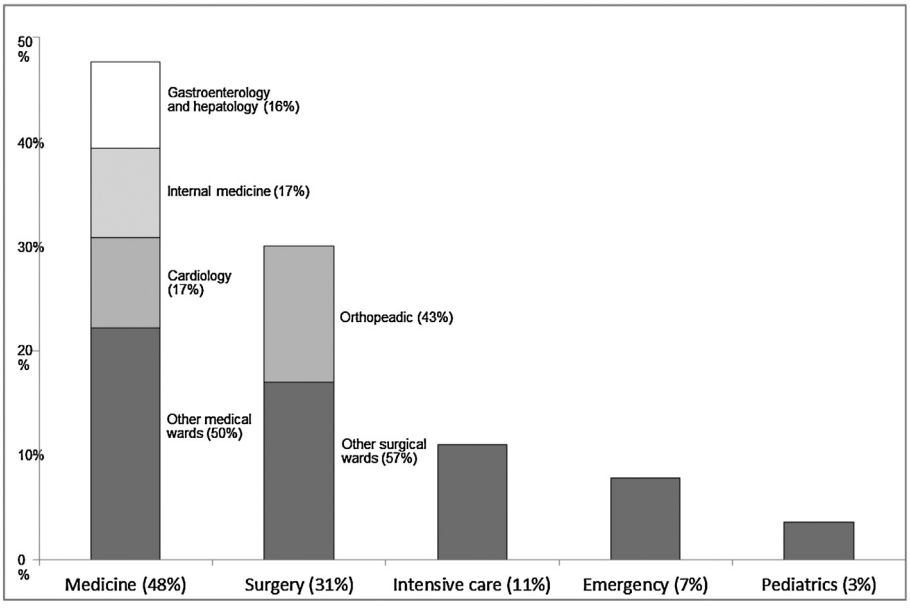

Figure 2. Specialties of the wards requesting advice from teams with transversal ID activity in France in 2013.
Spécialités des services demandant des conseils aux équipes médicales ayant une activité d'infectiologie transversale en France en 2013.

Table 2
Staffing of transversal ID activity in France in 2013.
Personnels dédiés à l'activité d'infectiologie transversale en France en 2013.

	All hospitals			University hospitals			Non-university hospitals			
	n/N	% or median	95% CI or IQR	*n/N*	% or median	95% CI or IQR	*n/N*	% or median	95% CI or IQR	*P*
Median number of acute beds in medical-surgical and obstetrics sectors		677	443–1064		1062	812–1287		473	290–606	<0.001
Median number of full-time physicians dedicated to transversal ID activity		0.8	0.3–1		1	0.5–1.15		0.5	0.25–1	0.003
Teams with a full-time physician dedicated to transversal ID activity	16/65	25%	15–37	11/31	36%	19–55	5/34	15%	5–31	0.052
Specific funding for the full-time physician dedicated to transversal ID activity	6/16	38%	15–65	6/11	55%	23–83	0/5	0%	0–52	0.093
Median number of physicians participating in permanent transversal ID consultancy activity		4	3–6		6	4–7		3	2–5	0.014
24/7 transversal ID consultancy activity	17/65	26%	16–39	14/31	45%	27–64	3/34	9%	2–24	0.001
Status of staff ensuring transversal ID activity										
MD, PhD	23/154	15%	10–22	21/102	21%	13–30	2/52	4%	0–13	0.006
MD	59/154	38%	31–46	28/102	27%	19–37	31/52	59%	45–73	<0.001
Fellow	26/154	17%	11–24	24/102	23%	16–33	2/52	4%	0–13	0.002
Assistant	21/154	14%	9–20	10/102	10%	5–17	11/52	21%	11–35	0.052
Junior physician or medical student	21/154	14%	9–20	18/102	18%	11–26	3/52	6%	1–16	0.042
Other	4/154	2%	1–7	1/102	1%	0–5	3/52	6%	1–16	0.112
Shared transversal ID activities										
Bacteriologists	40/65	62%	49–73	20/31	65%	45–81	20/34	59%	41–75	0.638
Pharmacists	32/65	49%	37–62	14/31	45%	27–64	18/34	53%	35–70	0.531
Infection control physicians	30/65	46%	34–59	11/31	36%	19–55	19/34	56%	38–73	0.099

Table 3
Cross-charging and recovery of funds to teams for transversal ID consultancy activity in France in 2013.
Valorisation et reversement financier de l'activité de consultation d'infectiologie transversale aux équipes médicales en France en 2013.

	n/N	%
Type of funding		
For in-hospital consultancy activity		
Cross-charging as a patient consultation	16/21	76
Overvaluation of clinical coding acts only	1/21	5
Cross-charging as a consultation + overvaluation of clinical coding acts	3/21	14
Cross-charging as a consultation + funding for MERRI	1/21	5
For external consultancy activity		
Contract with the external structure	2/5	40
Payment of physician time by the external structure	3/5	60
Recovery of funds		
By the team only	3/5	60
By the team + funding of MIG	1/5	20
Global funding of the team	1/5	20

MERRI: missions of teaching, research, and innovation; MIG; missions of general interest.

In-hospital transversal ID consultancy activity was cross-charged by 21 teams (32%), 6 in university hospitals and 15 in non-university hospitals ($P = 0.033$). Five teams (10%) invoiced ID activity performed in external structures (Table 3). The relevant funds were recovered by the teams concerned in 8 cases (2 in university hospitals and 6 in non-university hospitals).

4. Discussion

This survey provides the first description of transversal ID activity in French university and non-university hospitals. At the time of the survey (i.e., 2013), transversal ID activity was still relatively recent, having existed for a median of only 6 years. Transversal ID consultancy activity was present in 98% of the responding hospitals, and 77% of the teams with transversal ID activity promoted antibiotic stewardship through guidelines or audits. Only 11 teams (17%) prepared an annual report on their transversal ID activity. The median staffing level for this transversal ID activity was 0.8 full-time physician equivalents. Specific funding for ID physicians dedicated to transversal ID activity was provided in only 6 university hospitals (9%). Only 32% of teams cross-charged their in-hospital transversal ID consultancy activity, and 10% their external ID activity.

The main transversal ID activity of the teams consisted in providing specialist advice to other hospital wards and participating in specialized staff meetings, especially with orthopedic surgery teams. Most requests for ID advice came from medical and surgical departments, as observed in other studies [12–14]. The existence of multidisciplinary meetings in orthopedic surgery wards, especially in hospitals managing complex bone and joint infections, may explain why these departments made the largest number of requests for advice. Transversal ID consultancy activity needs to be better-recognized and more widely used by intensive care units, emergency departments, and hematology and cancer wards, which often encounter complex clinical situations as well as a high prevalence of bacterial resistance and

substantial antimicrobial drug expenditure. However, uptake of ID specialist advice is highly dependent on relationships among physicians, the working habits of individual wards, and the availability of transversal ID consultancy teams. Only a few of the responding teams had established strong links with private clinics or general practitioners. In contrast, studies of French and Swiss university hospitals indicate that about half the requests for ID advice came from external structures [12,15].

The second major transversal ID activity of the teams was to promote antibiotic stewardship. With the rapid increase in bacterial resistance, especially due to extended-spectrum β-lactamase (ESBL) production by urinary pathogens, antibiotic stewardship is crucial to optimize antibiotic prescription, especially to avoid inappropriate use of carbapenems and to choose appropriate alternatives. Good antibiotic stewardship leads to less overall and inappropriate antimicrobial use, lower drug costs, reductions in *Clostridium difficile*-associated disease, and less antimicrobial resistance [16]. In our study, 23% of the teams (19% in university and 26% in non-university hospitals) had yet to implement antibiotic stewardship programs, whereas Ireland and the United Kingdom have antimicrobial prescribing policies in most of their hospitals [17,18]. As in France, effort must intensify in America and Canada [19,20]. However, national comparisons are hindered by the use of different definitions of antibiotic stewardship.

In September 2013, the French authorities [21] recommended the designation of an antimicrobial therapy lead specialist in all hospitals, dedicated to providing advice and promoting antibiotic stewardship. The recommended staffing level is proportional to the number of beds: 30% of a full-time physician equivalent for a 400-bed acute care hospital, and 10% for a 400-bed long-term care facility (rehabilitation, psychiatric, or elderly care). In our study, the median number of physicians dedicated to transversal ID activity was 0.8 full-time equivalents. With a median of 677 acute beds per responding hospital, this seems to comply with current regulations. However, in view of the various missions incumbent on antimicrobial therapy lead specialists, we consider that one full-time physician would be necessary for a 700-bed acute care hospital, as is the case for infection control physicians. Moreover, we observed that the time devoted to transversal ID activity was often shared between several ID physicians, internists, pharmacists, bacteriologists, and infection control physicians. Only 25% of the responding teams had a full-time physician dedicated to transversal ID activity. Permanent 24/7 transversal ID consultancy activities were available in only one-quarter of hospitals (mainly university hospitals), probably owing to a lack of staff. Large hospitals with dedicated ID wards could cooperate with smaller hospitals in the same catchment area by creating a shared transversal ID team, thus covering the needs for transversal ID activity in all hospitals.

Transversal ID teams should include students and fellows, as this activity covers all aspects of IDs and is therefore highly instructive. Encouragingly, in the university hospitals that responded to our survey, 40% of physicians participating in transversal ID activity were students or fellows. Only half the responding teams involved bacteriologists, pharmacists, and infection control physicians; yet collaboration among all specialists involved in the fight against antimicrobial resistance is crucial.

Only 9% of responding teams provided dedicated funding for a full-time transversal ID physician. The 2013 decree [21] mandating the presence of an antimicrobial therapy lead specialist in all French hospitals should improve this situation. In our opinion, the creation of transversal ID teams requires the specific recruitment of an ID physician, rather than diverting existing physicians from their traditional ID activities, that remain essential in case of patient isolation, complex infections, and emerging diseases for example. Specific funding could be offset by the cost savings generated by a more appropriate use of antibiotics. Indeed, several studies [8–10,22,23] have shown that dedicated ID physicians can reduce unnecessary use of expensive antibiotics and tests, as well as overall antibiotic consumption. They can also promote an earlier switch to the oral route, help prevent adverse effects, and shorten the hospital stay.

While French hospital budgets are mainly funded by direct reimbursement of charges for patient hospitalization, significant supplementary funding comes from government grants, aimed among other things at promoting innovative care and multidisciplinary actions. The latter type of funding would be more appropriate for financing transversal ID teams. Also, advice on antibiotic usage could be provided remotely to both hospital wards and external medical structures, through a telemedicine system for example, and could be charged in the same way as a patient consultation. Sustainable funding is crucial for the development of transversal ID activity, several studies having shown that a lack of resources is the main obstacle to the implementation of antibiotic stewardship [18,19,24,25].

This lack of specific funding is aggravated by the fact that few teams cross-charged their transversal ID consultancy, especially in university hospitals. In addition, the funds generated by cross-charging were not always recovered by the teams concerned. As a prerequisite for proper funding, all teams should quantify and report their transversal ID activity. There is currently no nationwide system for transversal ID activity data collection and reporting, whereas this is the case for infection control teams. Standardized reporting by all hospitals would permit benchmarking between hospitals, with increasing objectives over the years.

This study has certain limitations. First, although more than two-thirds of French university hospitals responded to the survey, this was the case of only 5% of general hospitals and 3 private hospitals, as our sample did not include hospitals without a declared ID physician. Second, we only collected the number of requests for advice received by the teams and not the number of requests that resulted in a bedside consultation. Third, this was a declarative study without mandatory participation, and this might have somewhat overestimated the proportion of hospitals with organized transversal ID activity, as those without this type of activity may have decided not to participate.

In 2013, transversal ID activity was still in its infancy in France. This survey highlighted shortcoming in the management of antimicrobial stewardship, dedicated funding of antimicrobial therapy lead specialist, cross-charging, and collaboration with

other specialists involved in the fight against antibiotic resistance. Transversal ID activity should be regularly evaluated in order to promote its implementation in all French hospitals.

Contributors

V. Perut performed the statistical analysis and wrote the article.

H. Aumaître contributed to the study conception, designed the protocol, collected the data, participated in data interpretation, and made significant modifications to the article during the reviewing phase.

D. Salmon Ceron contributed to the study conception, designed the protocol, participated in data interpretation, and wrote the article.

E. Pichard, O. Patey, P. Andre, Y. Welker, O. Bouchaud, and C. Rabaud contributed to the study conception and reviewed the final version of the article.

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Disclosure of interest

The authors declare that they have no competing interest.

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Case report

Haemophilus parainfluenzae endocarditis in young adults

Endocardite à Haemophilus parainfluenzae *chez le jeune adulte*

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1. Introduction

Infective endocarditis is most often severe and compromises patient survival. Endocarditis mortality is estimated at 20% [1]. With the exception of intravenous drug users, endocarditis usually occurs in elderly patients presenting with comorbidities and implanted devices such as pacemaker, venous access device, or prosthesis. Infective endocarditis diagnosis is usually established in patients presenting with a long-lasting fever, after having diagnosed septic metastases such as septic splenic embolism or spondylitis, or after having discovered vegetation during transthoracic echocardiography following bacteremia. International and French guidelines highly recommend performing a transthoracic echocardiography when blood cultures are positive for fungi or *Staphylococcus aureus* [1]. Although well-known pathogens such as *Candida* spp. and *S. aureus* are commonly involved in endocarditis, other uncommon pathogens such as *Haemophilus parainfluenzae* may also be responsible for endocarditis [2]. These latter pathogens need to be better known to allow for a prompt diagnosis, better medical treatment, and improved outcome. We report the case of a 33-year-old female patient with no relevant medical history admitted to the emergency department of Lille University Hospital for fever (Fig. 1).

2. Case report

The patient spent 14 days in the south of France in August. Two days after returning to Northern France, she presented with fever, rigors, chills (39–39.5 °C), and a flu-like syndrome with headache and myalgia. She consulted her general practitioner the next day and was prescribed paracetamol (Fig. 1) and a blood test. The results of the blood test showed an inflammatory syndrome with elevated C-reactive protein (CRP) to 5.4 mg/dL, leukopenia with lymphopenia (900–1000/mm^3), and a decreased platelet count to 105,000/mm^3. A diagnosis of viral infection was suggested. Fever decreased the next day and the patient was afebrile with an improved general status. Fever and headache recurred one day later and the patient was seen at the emergency department of a local hospital. No meningeal syndrome or new clinical symptom was observed at physical examination. Blood tests were performed and showed an increased CRP to 8.0 mg/dL, a decreased platelet count to 95,000/mm^3, and persistence of lymphopenia with a moderate decrease in the neutrophil count (1200/mm^3). The patient was discharged home with a symptomatic treatment (Fig. 1). A transient improvement was observed but she was admitted to the emergency department of Lille University Hospital (Fig. 1) two days later for strong headache, persistent fever, nausea, vomiting, and retro-ocular pain. The lumbar puncture performed was normal (2 cells/mm^3) and the patient was transferred to the infectious disease department. Her medical history identified exposure to mosquitoes during her time in the south of France, where Dengue cases were

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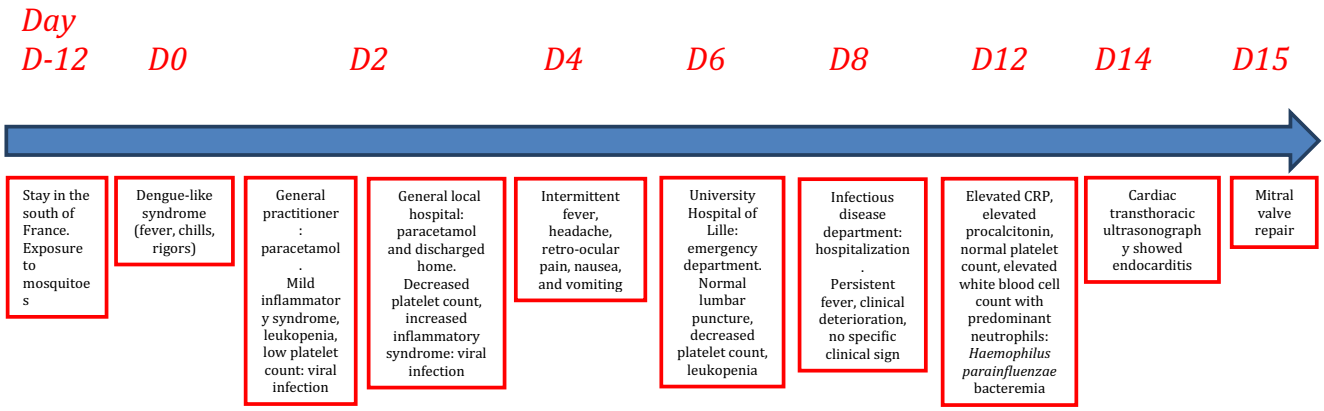

Fig. 1. Patient's medical journey.
Parcours médical du patient.

reported. Her temperature curve showed a biphasic and intermittent fever. Blood tests were performed and revealed a decreased platelet count with a nadir on Day 7 (77,000/mm^3), leukopenia, and elevated CRP to 10 mg/dL. Urine and blood polymerase chain reaction (PCR) were not performed on Day 7. Dengue serological test was negative twice. The patient remained in the hospital due to the absence of apyrexia after 48 h, and rapidly presented with persistent fever (38–38.5 °C) and clinical deterioration (Fig. 1). Urine analysis and chest X-ray were normal, and the physical examination revealed headache and earache with normal otoscopy. The results of the blood test showed an elevated CRP to 21.7 mg/dL, elevated procalcitonin to 4 ng/mL, normal platelet count (165,000/mm^3), and elevated white blood cell count (13,000/mm^3) with predominant neutrophils (9500/mm^3) (Fig. 1). A blood culture positive for a Gram-negative bacterium was obtained three days later. Intravenous cefotaxime was immediately administered. The mass spectrometry (MALDI-TOF, Bruker Corporation) identified *H. parainfluenzae*. Amoxicillin 200 mg/kg/day was prescribed. Although the patient was treated with an adequate antimicrobial therapy, her fever persisted after 48 h and transesophageal echocardiography showed a mitral valve endocarditis with a 20 mm vegetation, severe valve destruction, and grade-3 mitral insufficiency (Fig. 2). Intravenous levofloxacin (750 mg) was added to the antimicrobial regimen and the patient was transferred to the cardiology intensive care unit. The results of a cerebral CT scan were normal and the patient underwent emergency mitral valve repair without valve replacement. She was treated for six weeks with ceftriaxone, rifampicin, and ciprofloxacin. The PCR in the valve abscess pus was positive for *H. parainfluenzae*. During the follow-up period, the patient presented with *S. aureus* bacteremia after one month of treatment. It was related to a catheter infection, with no recurrence, and the patient was discharged home.

After a three-month-follow-up, the patient did not present with any recurrence of fever. The median sternotomy healed properly and cardiac ultrasonography controls were normal. The patient no longer presents with clinical general or cardiac failure symptoms. She had been implanted with an intrauterine device (IUD) two years before. She was evaluated by a gynecologist

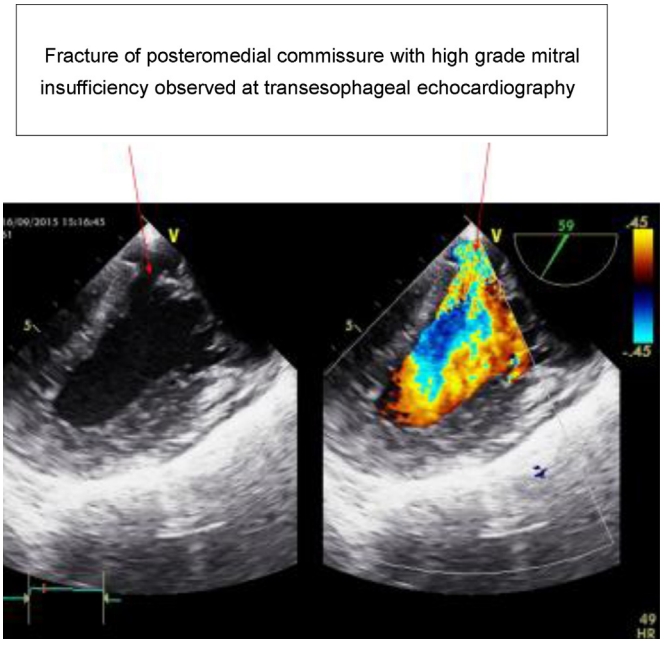

Fig. 2. Results of the transesophageal echocardiography.
Résultats de l'échographie transœsophagienne.

and no local complication was observed. The IUD was removed before cardiac surgery and after bacterial identification. IUD culture and PCR were negative.

3. Discussion

Gram-negative endocarditis is uncommon. It accounts for 1 to 3% of endocarditis cases [1]. Gram-negative bacteria such as Enterobacteriaceae and *Pseudomonas aeruginosa* are usually responsible for infective endocarditis but rare and fastidious bacteria may be involved (i.e., bacteria from the HACEK group [3]: *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens, Kingella kingae*, and *Haemophilus* spp.). *H. parainfluenzae*, mainly involved in genital and urinary tract infections, is also a commensal bac-

terium of the upper respiratory tract responsible for pneumonia, arthritis, meningitis, and in rare cases for endocarditis [2,4]. Several cases of *H. parainfluenzae* endocarditis have been reported in the literature [5,6]. There are only two articles, respectively reporting 40 case patients before 1980 and 42 case patients of *Haemophilus* spp. endocarditis between 1983 and 1995 [2]. The authors of the latter study isolated *H. parainfluenzae* in 26 patients. The bacterium seemed to be the major subspecies involved in infective endocarditis. The authors of another study reported seven cases of *H. parainfluenzae* endocarditis [7]. Common characteristics of these patients were young age (mean age between 27 and 40 years) and no medical history or comorbidity [2,8]. The hallmark of their recent medical history was always fever. Mean duration of symptoms before diagnosis was 30 days. No pathological cardiac murmur or congestive heart failure signs were observed. Portal of entry remained unknown in 80% of cases [2,8]. Native mitral valve was most frequently affected (70%) and half of the patients required valve replacement [2,8]. The overall mortality was lower (10%) than that observed with other pathogens, but secondary complications such as brain embolism often led to diagnosis (25% of cases) because of diagnostic difficulties [2,8]. This decreased mortality and the absence of cardiac failure may be attributed to young age and to the absence of comorbidity in this subgroup of patients.

Consistent with these observations, our patient was 33 years old and presented with a history of prolonged fever and a destructive native mitral valve endocarditis (Fig. 2) with no heart failure (Fig. 1). Cardiac transthoracic ultrasonography was performed and allowed for a prompt diagnosis of endocarditis, although no cardiac sign was observed.

4. Conclusion

H. parainfluenzae remains a rare cause of infective endocarditis. Similar to *S. aureus* or *Candida* spp., the isolation of *H. parainfluenzae* from blood cultures must immediately lead to transthoracic echocardiography.

Authors' contributions

E.F and O.C. wrote the article.
K.F, B.G, G.S, and E.F. reviewed the article.
E.F, O.C, A.V., and G.S took care of the patient.

Disclosure of interest

The authors declare that they have no competing interest.

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Cas clinique

Granulomatose disséminée nécrosante liée à histoplasma capsulatum

Histoplasma capsulatum disseminated necrotizing granulomatosis

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1. Présentation

Un homme de 35 ans est admis en réanimation médicale, à Marseille (France), pour détresse respiratoire aiguë. Il s'agit d'un patient russe d'origine mais ayant toujours vécu en France, marié (famille recomposée avec 3 enfants), présentant un tabagisme ancien et vivant entouré d'un chat, de poules et de canards. Le patient est utilisateur régulier de plantes médicinales et d'huiles essentielles. Il travaille dans l'empaquetage de plantes médicales. On retrouve à l'interrogatoire une notion de séjour de 6 mois en Équateur 4 ans avant son admission ainsi que plus récemment en Bulgarie, Roumanie, Espagne, Canada, Grèce et Norvège.

L'histoire commence un an avant l'admission en réanimation par l'apparition d'une dyspnée et d'une toux chronique associées à des expectorations purulentes, des épisodes fébriles et une perte de poids modérée (3 kg). Le premier bilan étiologique réalisé six mois après le début des symptômes en pneumologie concluait à une pneumopathie interstitielle granulomateuse diffuse. La radiologie thoracique (Fig. 1A et B) montrait une atteinte interstitielle à prédominance péribronchovasculaire associée à des opacités réticulomicronodulaires et du verre dépoli prédominant dans les lobes supérieurs, ainsi qu'à de multiples adénopathies médiastinales supracentimétriques partiellement calcifiées. Les explorations fonctionnelles respiratoires mettaient en évidence un trouble ventilatoire mixte (Tiffeneau 59 %, VEMS 50 % et CPT 70 %) associé à un trouble de la diffusion alvéolocapillaire (TLCO 52 %). Le lavage broncho-alvéolaire (LBA) objectivait une alvéolite neutrophilique à 20 % avec explorations microbiologiques négatives (examen direct et cultures bactériologiques, mycobactériologiques, mycologiques et parasitologiques). Il n'y avait pas d'élément atypique à la cytologie, pas plus qu'à l'examen histologique des biopsies bronchiques. Les bilans sanguins immunologiques étaient également négatifs (anticorps antinucléaires, anti-ADN natifs, anti-CCP, facteur rhumatoïde, ANCA). La sérologie VIH est négative. La biopsie pulmonaire chirurgicale retrouvait à l'examen anatomopathologique une pneumopathie interstitielle granulomateuse épithélioïde et gigantocellulaire focalement nécrosante et une documentation microbiologique négative. L'hypothèse d'une tuberculose a été retenue et une quadrithérapie antituberculeuse a alors été instaurée. L'apparition d'une cytolyse hépatique conduisait finalement à une association rifampicine, clarithromycine et éthambutol. La recherche de mycobactéries au LBA et sur la biopsie pulmonaire à l'examen direct, en culture et en PCR restant négative, le traitement antibiotique était arrêté à 3 mois, sans aucune amélioration clinicoradiologique notable.

L'hypothèse diagnostique d'une sarcoïdose pulmonaire stade IV est alors posée malgré l'histologie atypique. Une

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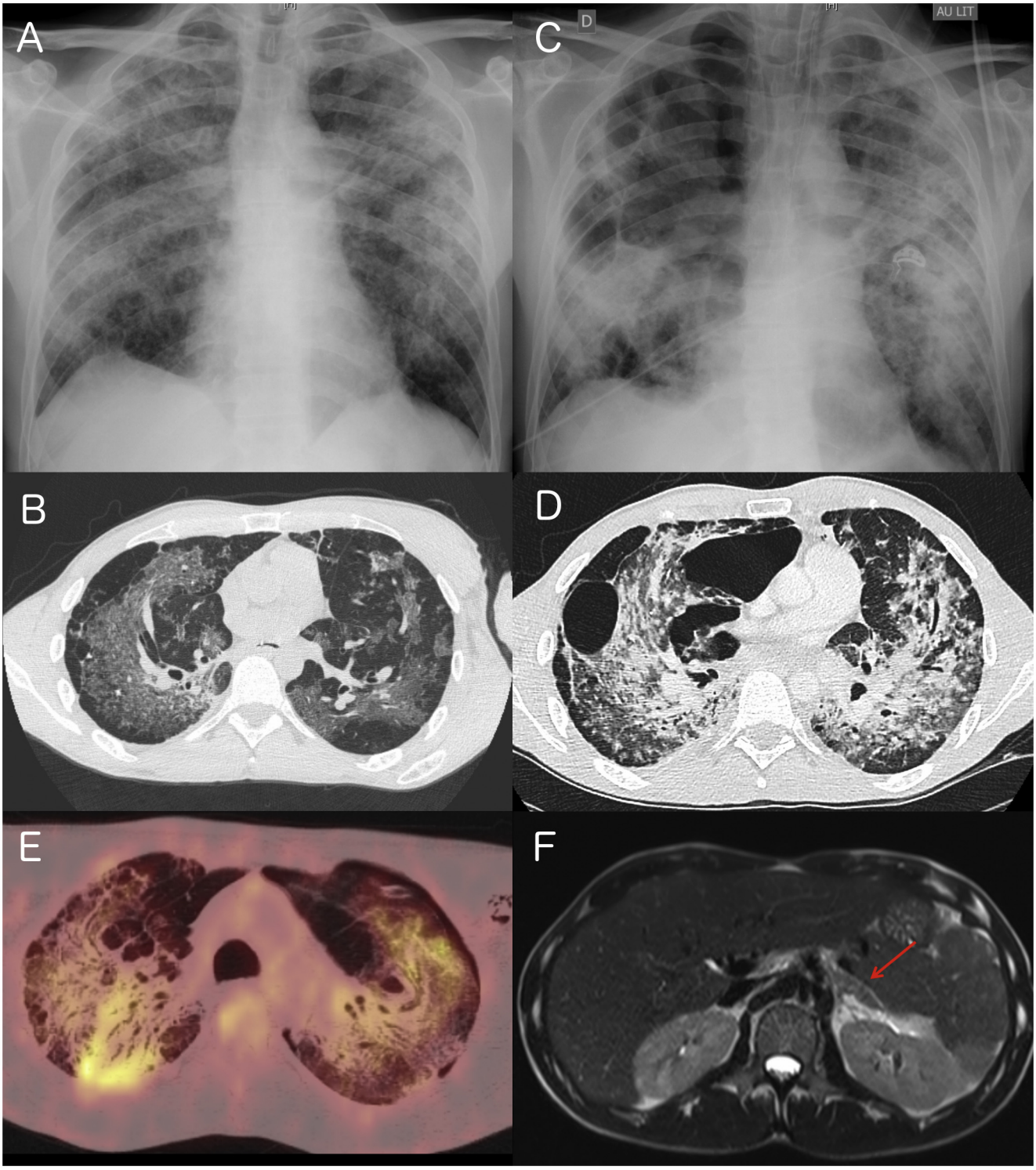

Fig. 1. Radiographie thoracique, scanner et TEP. A et B. Syndrome interstitiel pulmonaire radiologique diffus avec verre dépoli au scanner. C et D. Évolution fibrosante radiologique avec destruction parenchymateuse à 3 mois du début de la prise en charge. E. TEP-TDM mettant en évidence un hyper-métabolisme des lésions pulmonaires. F. IRM abdominale montrant un aspect d'hyperplasie surrénalienne gauche sans spécificité.
Chest x-ray, scan, and PET scan. A and B. Radiological diffuse pulmonary interstitial syndrome with ground glass on scan. C and D. Radiological fibrotic changes with parenchymal destruction 3 months after treatment initiation. E. PET-scan showing a hyper-metabolism of lung injuries. F. Abdominal MRI showing signs of left adrenal hyperplasia without any specificity.

corticothérapie à 1 mg/kg/j est débutée. L'évolution clinique est défavorable sur le plan respiratoire. L'imagerie thoracique (Fig. 1C et D) s'aggrave, avec majoration de l'atteinte réticulonodulaire et aspects de condensation dans les zones auparavant en verre dépoli ainsi que l'apparition d'une destruction bulleuse prédominant aux apex. Une TEP-TDM est réalisée (Fig. 1E) et révèle un hypermétabolisme marqué des images de condensation ($SUV_{max} = 6,5$), un hypermétabolisme modéré des ganglions médiastinaux ($SUV_{max} = 3$) et un hypermétabolisme intense et pathologique de la surrénale gauche ($SUV_{max} = 6$). Une IRM abdominale (Fig. 1F) confirme une hyperplasie surrénalienne gauche sans élément en faveur d'un adénome ou d'un phéochromocytome.

Les suites sont marquées par un épisode d'exacerbation de dyspnée fébrile, traité de manière probabiliste comme une pneumonie nosocomiale par pipéracilline/tazobactam et amikacine. Devant l'apparition d'une détresse respiratoire aiguë, le patient est hospitalisé en réanimation, rapidement intubé et mis sous ventilation mécanique invasive. Devant l'absence d'amélioration clinique et la négativité des prélèvements microbiologiques antérieurs, une nouvelle biopsie pulmonaire chirurgicale est réalisée ainsi qu'un nouvel LBA.

Le diagnostic d'histoplasmose a alors été affirmé devant des PCR en temps réel positives sur ces deux derniers examens, ainsi que la présence d'histoplasmes dans leur forme levure (éléments ovoïdes à noyau latéral) à l'examen direct par coloration de May-Grünwald-Giemsa du LBA (Fig. 2A). L'analyse anatomopathologique de cette deuxième biopsie retrouve une atteinte hétérogène du poumon par la mise en évidence de microgranulomes avec nécrose centrale sans cellules géantes constitués d'histiocytes palissadiques en périphérie (Fig. 2B et C). L'immunohistochimie réalisée avec l'anticorps anti-CD1A, en faveur d'une histiocytose langerhansienne, est négative. Les colorations spéciales sont non contributives. Un traitement par amphotéricine B liposomale associé à une corticothérapie à 1 mg/kg/j est introduit. L'évolution clinique sera défavorable, malgré la mise en place du traitement antifongique et d'une assistance respiratoire extracorporelle, avec une évolution rapide vers une défaillance multiviscérale et le décès 48 h après l'introduction du traitement.

2. Discussion

Du fait d'une localisation hors d'une zone d'endémie [1] et de notion d'absence de voyage « récent », chez un patient immunocompétent, le diagnostic d'histoplasmose pulmonaire n'a pas été évoqué d'emblée. Ces deux éléments ont constitué la difficulté à établir le diagnostic, du fait de son absence d'évocation et donc de recherche spécifique. Ce diagnostic difficile a conduit au décès du patient.

Pourtant, a posteriori, la présentation clinique est assez classique et il existe la notion de voyages « anciens » en zone endémique. Le tableau initial est celui d'une dyspnée et d'une bronchorrhée fébrile avec atteinte interstitielle pulmonaire granulomateuse nécrosante et altération de l'état général. L'aggravation après corticothérapie avec, d'une part, une évolution vers la destruction pulmonaire, et d'autre part, l'apparition d'une image surrénalienne sont évocateurs d'une évolution de l'histoplasmose pulmonaire vers une forme chronique et disséminée grave, favorisée par l'immunodépression induite [2].

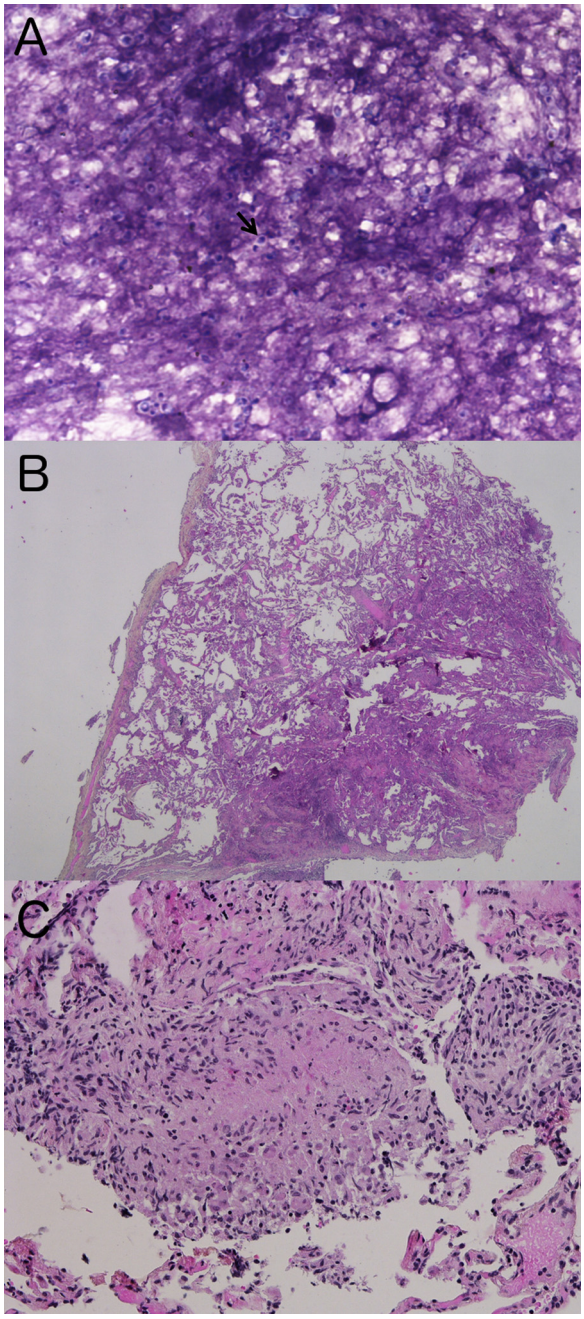

Fig. 2. Coupes histologiques. A. Examen direct du LBA montrant les histoplasmes (flèche) dans leur forme levure (éléments ovoïdes à noyau latéral) par coloration de Mary-Grünwald-Giemsa. Analyse histologique (B. Faible. C. Fort grossissement) retrouvant une atteinte hétérogène du poumon et la présence de microgranulomes avec nécrose centrale, sans cellule géante, constitués d'histiocytes palissadiques en périphérie.
Histological sections. A. Direct examination of BAL showing histoplasma (arrow) in their yeast form (ovoid elements with lateral nucleus) by Mary-Grünwald-Giemsa staining. Histological analysis (B. Weak. C. Strong magnification) revealing a heterogeneous lung damage and the presence of microgranulomas with central necrosis, without giant cells, made of histiocytes in palisade at the periphery.

La tuberculose, principal diagnostic différentiel de l'histoplasmose pulmonaire, a été évoquée et dans un premier temps traitée chez ce patient. La confusion avec la sarcoïdose n'est pas rare et plusieurs cas sont rapportés dans la littérature [3], pouvant conduire, comme pour ce patient à une franche aggravation lors de la mise sous immunosuppresseurs.

Les moyens diagnostiques biologiques disponibles sont multiples mais généralement non réalisés en routine, surtout en zone non endémique comme la France. Certains peuvent parfois nécessiter un œil expert et entraîné comme l'examen direct réalisé sur produits pathologiques (LBA, LCR, biopsies, etc.). Après coloration au May-Grunwald-Giemsa, il est mis en évidence de petites levures de 3 μm de diamètre, ovalaires, avec un halo clair (correspondant à la membrane). Les levures sont également gram positif et colorées en rouge par le Periodic-Acid-Schiff. Les diagnostics différentiels peuvent être le *Candida* sp., le *Cryptococcus neoformans* et le *Pneumocystis jirovecii*, ainsi que des artefacts de coloration. La culture fongique sur milieu de Sabouraud, entre 25 et 30 °C, représente la méthode la plus sensible pour le diagnostic, mais nécessite des délais longs (2 à 6 semaines) et n'est réalisée qu'en laboratoire spécialisé. L'analyse anatomopathologique retrouve très fréquemment des granulomes ou infiltrats lympho-hystiocytaires, l'évolution se faisant, comme la tuberculose, vers une nécrose caséiforme. Une forme anergique est possible chez l'immunodéprimé avec une réaction tissulaire faible ou nulle. La détection antigénémique est très contributive chez les patients immunodéprimés et chez les patients présentant une forme grave [4]. Elle est réalisée sur plasma ou urines et peut être complétée par une recherche sur LBA [5]. La sensibilité est similaire entre recherche urinaire et plasmatique, en revanche, des réactions croisées existent avec d'autres infections fungiques (blastomycoses, aspergilloses). Le diagnostic par PCR n'est pas utilisé en routine. Une étude réalisée sur prélèvement pulmonaire [6] retrouve que 73 % des échantillons positifs à la culture étaient positifs à la PCR en temps réel pour *Histoplasma capsulatum*. Enfin, les tests sérologiques sont limités par une positivité persistante des années après exposition [7], peuvent être également négatifs chez le sujet immunodéprimé. Cependant, leur utilisation peut avoir un intérêt hors zone d'endémie avec une clinique compatible et couplé aux autres tests biologiques.

L'histoplasmose est liée à deux variétés pathogènes d'*Histoplasma* sp., présents dans de nombreuses régions du monde mais absente en Europe. La plus commune est *H. capsulatum* var. *capsulatum* qui est endémique aux États-Unis, Amérique du sud, Asie et Afrique, et *H. capsulatum* var. *duboisii* endémique uniquement en Afrique. Du fait de sa croissance dimorphique (phase mycélienne à températures ambiantes produisant les spores et phase levurique à température corporelle), il n'y a pas de contamination inter-humaine. La contamination se fait donc par inhalation de poussières riches en spores [1] (contact avec déjection d'oiseau, de chauve-souris, visite de grotte). La maladie pouvant être due aussi bien à une infection exogène qu'à une réactivation d'un foyer latent depuis des années, l'historique du patient, notamment avec ses voyages dans des zones endémiques (Amérique du sud) est compatible avec une inoculation latente. L'importation de nombreuses plantes séchées et en poudre d'origine incertaine peut être également suspectée, bien qu'une recherche n'ait pas été faite dans ce sens et qu'aucun cas n'ait été décrit dans la littérature. Enfin, le contact rapproché avec des poules aurait pu être suspecté, mais peu probable car le patient ne résidait pas en zone endémique.

L'histoplasmose pulmonaire est une pathologie rare en France, mais doit être évoquée dans le diagnostic différentiel des pneumopathies interstitielles granulomateuses nécrosantes, même chez le sujet immunocompétent, surtout en cas d'existence de facteurs de risques épidémiologiques, comme la notion de voyage en zone endémique, même ancien. Les outils diagnostics tels que la détection d'antigène et la PCR en temps réel permettent un diagnostic plus rapide que la culture.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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Cas clinique

Endocardite à *Finegoldia magna*

Finegoldia magna *endocarditis*

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Keywords: Endocarditis; *Finegoldia magna*; Mass spectrometry

1. Introduction

Finegoldia magna (ex *Peptostreptococcus magnus*) est une bactérie à Gram positif anaérobie dont l'habitat naturel est la peau et les voies aéro-digestives supérieures [1]. Elle est notamment reconnue responsable d'infections respiratoires hautes et basses, ostéo-articulaires, en particulier sur matériel [2–4]. À ce jour, nous n'avons retrouvé que huit cas d'endocardite à *F. magna* publiés. Parmi ces derniers, dans deux cas seulement la bactérie a été isolée des hémocultures (dans un cas également de culture de valve) [5,6], dans les six autres le diagnostic n'a été obtenu que sur les prélèvements peropératoires [7,8]. Nous rapportons, ici, un nouveau cas diagnostiqué sur les hémocultures après identification par spectrométrie de masse, 4 mois après la pose d'une bioprothèse aortique.

2. Cas clinique

Une femme âgée de 78 ans a été admise en urgence pour dyspnée d'apparition brutale et sensation de chaleur. Le diagnostic d'œdème aigu du poumon a été porté. Il existait un contexte de syndrome inflammatoire modéré et d'asthénie depuis un mois. Il s'agissait d'une patiente diabétique (diabète insulino-requérant) et porteuse d'une bioprothèse aortique posée 4 mois plus tôt en raison d'un rétrécissement aortique serré. Les suites postopératoires avaient été simples. Dans ses antécédents, on relevait aussi, plusieurs années auparavant, une cholécystectomie et une thyroïdectomie depuis laquelle elle recevait un traitement substitutif par lévothyroxine sodique (Lévothyrox®) 75 µg/j. Le reste de son traitement comprenait de l'acétylsalicylate de DL-lysine (Kardégic®) 75 mg/j, de l'insuline lispro (Humalog Mix 50®) 6 unités le matin, 10 à midi et 14 le soir, de l'amitriptyline 25 mg/j et du pantoprazole 20 mg/j.

À l'entrée, sa température, non contrôlée avant l'admission, était de 38,2°C. La fréquence respiratoire était de 23/minute, la fréquence cardiaque de 112/minute, avec un rythme régulier, la tension artérielle est de 140/80 mmHg. Le poids de la patiente était de 72 kg pour une taille de 1,64 m soit un IMC de 26,8 kg/m^2. L'auscultation montrait la présence de râles crépitants diffus bilatéraux et d'un souffle d'insuffisance aortique non connu. L'examen neurologique était normal. Le bilan biologique sanguin montrait un taux de leucocytes à 13 900 dont 82 % de polynucléaires neutrophiles, un taux d'hémoglobine à 11,3 g/dL, une protéine C-réactive à 65 mg/L (N < 5) et une créatininémie à 69 µmol/L. L'ionogramme sanguin était normal. La recherche de troponine était négative et la *pro-brain natriuretic peptide* (pro-BNP) est à 546 pg/mL (N < 300). Trois paires d'hémocultures étaient prélevées à 30 minutes d'intervalle, chacune avec un flacon aérobie : BD Bactec Plus Aerobic/F® et un flacon anaérobie : BD Bactec Lytic Anaerobic/F®. La radiographie thoracique indiquait un syndrome interstitiel bilatéral prédominant aux bases. Une endocardite sur bioprothèse aortique était suspectée et une échographie trans-thoracique était pratiquée montrant une fraction d'éjection ventriculaire conservée, une hypertrophie ventriculaire gauche non obstructive avec un septum à 13 mm et un reflux aortique difficilement quantifiable.

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Il n'y avait pas d'autres anomalies visualisées, notamment pas de végétations mais il était précisé que la fenêtre échographique était de mauvaise qualité. Dès la réalisation de la troisième hémoculture, une antibiothérapie probabiliste par voie intraveineuse associant amoxicilline (2 grammes, toutes les 6 heures) et gentamicine (80 mg toutes les 12 heures) était débutée. Au troisième jour, les hémocultures poussaient uniquement sur les 3 flacons anaérobie, l'identification était effectuée dans la journée par spectrométrie de masse (Microflex Brucker Daltonique®). Les spectres obtenus étaient traités sur la base de données IVD Biotyper 2.3® et permettaient d'identifier un *F. magna*. Ce même jour, une échographie trans-œsophagienne (ETO) était pratiquée, elle confirmait le diagnostic d'endocardite en montrant un volumineux abcès de l'anneau aortique et une fuite périprothétique majeure. Il existait également une insuffisance mitrale cotée à ¾, sans végétation. L'avis d'un référent en infectiologie était demandé. La gentamicine était alors arrêtée et l'amoxicilline poursuivie à la même dose. L'antibiogramme allait confirmer la sensibilité à l'amoxicilline. La souche était résistante à la clindamycine. Le scanner thoraco-abdomino-pelvien ne montrait pas de foyer secondaire. Devant la gravité des anomalies valvulaires visualisées à l'ETO, il était décidé d'opérer la patiente rapidement. L'intervention avait lieu 3 jours après la réalisation de l'ETO. En peropératoire, il était confirmé la présence d'un abcès (détergé) de l'anneau, une désinsertion de la bioprothèse aortique et une fuite mitrale très importante. Un double remplacement valvulaire (double bioprothèse) était donc effectué. Les cultures des pièces opératoires demeuraient stériles à 15 jours. En postopératoire, la température déjà normalisée après 2 jours d'antibiothérapie restait normale et la *C-reactive protein* (CRP) après un pic à 157 mg/L, 2 jours après l'intervention allait décroître lentement pour se normaliser au bout de 5 semaines d'antibiothérapie. La durée totale de l'antibiothérapie par amoxicilline IV était de 6 semaines. L'ETO de contrôle, 4 semaines après la chirurgie, allait montrer un bon fonctionnement des prothèses valvulaires et l'absence d'images évocatrices d'endocardite. Une nouvelle évaluation clinique, biologique et échographie cardiaque 3 mois et 6 mois après l'arrêt du traitement antibiotique permettait de confirmer la guérison.

3. Discussion

Le premier cas publié d'endocardite à *F. magna* (sous le nom de *P. magnus*) remonte à 1985 [5]. Depuis, 7 cas supplémentaires ont été publiés à notre connaissance (concernant spécifiquement *P. magnus* ou *F. magna*) [6–8]. Nous rapportons donc, ici, le neuvième cas, le troisième diagnostiqué grâce aux hémocultures et le premier grâce à la spectrométrie de masse à partir des hémocultures [5,6]. Les autres cas ayant été diagnostiqués sur culture valvulaire, parfois grâce à l'aide de la biologie moléculaire (PCR ARN 16S) [6,8]. Il a été rapporté que la sensibilité des hémocultures dans la détection des bactériémies à *F. magna* serait dépendante du système utilisé [7]. Dans cette étude, il était démontré que *F. magna* poussait dans les systèmes Septi-Chek BHI-S® et Isolator® mais pas dans le système BacT/Alert®. Pour notre part, nous avons utilisé, avec succès, donc, le système automatisé Bactec FX®. L'intérêt de la spectrométrie de masse (MALDI-TOF) dans l'identification des anaérobies et, en particulier, de *F. magna* a déjà été démontrée [9]. Cependant, à notre connaissance, cette technique n'a jamais été appliquée au diagnostic d'endocardite à *F. magna*.

Si l'on exclut le premier cas, survenu chez un patient de 18 ans [5], l'âge moyen des patients, en incluant le cas présent, est de 56 ans. En dehors encore du premier cas publié [5], concernant une valve mitrale native, tous les autres sont survenus sur prothèse valvulaire comme celui que nous rapportons. La présence de pili à la surface de *F. magna* pourrait participer à sa pathogénicité, notamment dans les endocardites [10]. Le délai entre la date de mise en place de la prothèse valvulaire et la date de survenue des premiers signes d'infection varie de 2 semaines à 2 ans, il est inférieur ou égal à 3 mois dans tous les cas sauf un, la médiane se situant à 2 mois. La localisation est aortique dans 2/3 des cas. À l'échographie cardiaque, une fuite para-valvulaire est constatée dans environ 2/3 des cas et un abcès dans plus de la moitié des cas. Dans celui que nous rapportons, il s'agissait d'un volumineux abcès. Compte tenu de l'importance des dégâts valvulaires constatés dans l'ensemble des cas rapportés, y compris le nôtre, un traitement chirurgical a été nécessaire. Il est étonnant de constater que sur les 8 cas publiés antérieurement à celui-ci, le traitement antibiotique était constitué d'une association β−lactamine-inhibiteur de béta-lactamase dans 3 cas, alors que *F. magna* n'est pas sécrétrice de béta-lactamase et qu'en conséquence, les concentrations minimales inhibitrices (CMI) de l'amoxicilline seule ou associée à l'acide clavulanique sont identiques [2]. La pénicilline était utilisée, seule ou associée (soit au métronidazole, soit à la gentamicine [pourtant inactive sur *Finegoldia*]), dans 4 autres cas. Dans le cas que nous rapportons ici, c'est l'amoxicilline, seule, qui a été utilisée avec succès. Étant donné la rareté de ce type d'infection, la durée de traitement n'est pas codifiée. Par analogie aux recommandations concernant le traitement d'endocardite sur prothèse valvulaire due à d'autres pathogènes, nous avons opté pour une durée de 6 semaines. Parmi les 9 cas répertoriés, deux décès ont été rapportés, mais ils ne concernaient pas les cas les plus récents puisque survenus en 1995 et 2000. On peut également noter aussi que la vancomycine a été utilisée soit en deuxième ligne soit en première ligne dans ces 2 cas. Si le faible nombre de cas ne permet pas de dégager de statistiques significatives en défaveur de la vancomycine, néanmoins, malgré son activité démontrée in vitro, ceci incite à privilégier l'utilisation d'une pénicilline à chaque fois que cela est possible.

Les endocardites à *F. magna* sont rares, peut-être sous-diagnostiquées compte tenu de la faible rentabilité des hémocultures et de l'administration d'une antibiothérapie probabiliste souvent active sur cette bactérie avant l'intervention chirurgicale, dans la majorité des cas. Elles surviennent habituellement sur prothèse valvulaire. Le traitement chirurgical semble nécessaire dans la prise en charge thérapeutique compte tenu de la nature (abcès fréquents) et de l'étendue des lésions. Les pénicillines demeurent les antibiotiques de choix.

Contribution des auteurs

Éric Bonnet a rédigé le cas clinique.

Jean-Louis Galinier et Benoit Fontenel ont réalisé l'identification microbiologique et validé l'antibiogramme.

Bruno Dongay et Philippe Soula sont les médecins qui ont pris en charge le patient dans leurs unités de soins et qui en ont assuré le suivi en collaboration avec Éric Bonnet.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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Case report

Successful pediatric ECMO in a rare case of septic shock due to a community-acquired *Legionella* infection

ECMO et choc septique secondaire à une infection communautaire à Legionella *chez un nourrisson*

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Mots clés : Choc septique ; *Legionella* ; ECMO

1. Introduction

Legionnaires' disease (LD) is commonly considered to be a well-recognized cause of pneumonia in adults. Immunocompromised conditions are not systematic underlying diseases. LD accounts for 2 to 9% of adult community-acquired pneumonia case patients. The pediatric incidence of the infection is probably underestimated [1]. Rare cases of LD have been described in neonates, most of which were hospital-acquired [2].

Among more than 50 species of *Legionella*, *Legionella pneumophila* is associated with 90% of LD case patients and, within 15 serogroups (sg), *L. pneumophila* sg1 is responsible for more than 80% of cases worldwide. Modes of transmission include inhalation of aerosols or aspiration of water contaminated with *Legionella*. Showers, tap waters, and cooling towers are the most suspected sources of community-acquired pneumonia. We report the case of a neonate who contracted severe community-acquired LD that required a venoarterial extracorporeal membrane oxygenation (ECMO), and finally survived.

2. Case report

The patient is the second child of non-consanguineous parents both coming from Mali and living in France. Their first child is healthy. The mother gave birth at 38 weeks, by spontaneous vaginal delivery after normal pregnancy. Birth weight was 2,630 g (–1 SD). The neonatal period was marked by hypoglycemia and hypocalcemia, rapidly regressive.

After more than 3 weeks at home, at the age of 27 days, the patient developed respiratory failure with fever (38 °C) and biological inflammatory response. Standard chest X-ray showed upper right lobe pneumonia. He was initially treated in a medical ward with cefotaxime, vancomycin, and gentamicin. Non-invasive positive pressure ventilation was required 2 days later due to respiratory failure, associated with hemodynamic failure. He then presented with severe bradycardia due to bilateral pneumothorax before intubation. He was then transferred to our pediatric intensive care unit.

The first clinical evaluation revealed a septic shock with a heart rate of 206 b/min, blotches, and low diuresis despite norepinephrine. Pulmonary examination revealed a decrease in right breath sounds. Lactate was 5 mmol/L. Maximum C Reactive Protein (CRP) and procalcitonin levels were respectively 477 mg/L and 82.6 µg/L. No sign of disseminated intravascular coagulation, renal, hepatic, or pancreatic failure was observed. The chest X-ray confirmed the upper right lobe pneumonia.

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The patient initially received five fluid expansions, and continuous noradrenaline with hydrocortisone. He was ventilated by standard volumetric ventilation. A suprasystemic pulmonary arterial hypertension was detected and treated with inhaled nitric oxide and prostacyclin. Within 12 hours, refractory hypoxemia and hemodynamic failure developed, characterized by lactate increase and low diuresis. A venoarterial ECMO was initiated on day 2 after admission in our unit. Macrolide (clarithromycin) treatment was added on day 6 after initial empirical treatment with cefotaxime, vancomycin, and gentamycin.

Bacterial, mycological, parasitological, and viral detections were initially negative, with multiple blood cultures. Detection of urinary pneumococcal antigen was negative. A lumbar puncture could not be performed due to initial hemodynamic failure and extracorporeal circulation. Bronchoalveolar lavage (BAL) was performed on day 3. Conventional culture of BAL sampled on day 3 was sterile, polymerase chain reaction (PCR) amplification of the bacterial 16S rRNA gene and subsequent sequencing was performed. The presence of bacterial DNA in BAL was detected and RNA 16s sequencing was *L. pneumophila* specific. This was confirmed on day 18 (13 days after clarithromycin initiation) by specific culture of tracheal aspiration fluid, which showed *L. pneumophila* sg3 colonies after 10 days. Urinary detection of *L. pneumophila* sg1 antigen (Binax Now *Legionella*) was negative on day 18.

After 18 days in our unit, computed tomography showed lung abscess evolution (Fig. 1). As the incubation period for LD ranges from 2 to 10 days, environmental investigations were performed on water supply of the patient's private home. All samples were positive for *L. pneumophila* sg3 strains, which were the same as the ones found in the BAL, confirming that *L. pneumophila* infection was acquired at home.

Immunological investigations conducted showed possible inborn immunodeficiency. Total lymphocyte count was slightly low (2.6×10^9/L [$3.40–7.20 \times 10^9$/L]), with a decreased T CD4+ (0.520×10^9/L [$1.80–4.00 \times 10^9$/L]) and CD8+ lymphocyte count, with low percentage of T CD4+ naïve cells (37% [60–72%]), normal B and NK cells counts. T lymphocyte proliferative response to phytohemagglutinin (PHA) was normal, but the response to OKT3 (T lymphocytes proliferation test) was poor. Serum IgG levels were normal at the beginning of the disease but may have been from maternal origin. The patient had hypo-IgA serum levels (0.07 g/L [0.12–0.38 g/L]). Complement exploration C3, C4, and CH50 was normal (Table 1).

After 10 days of macrolide treatment (clarithromycin), an additional 5-day treatment was initiated on day 21 (azithromycin and levofloxacin) after confirmation of *Legionella* pneumonia. Other antibiotics were discontinued on day 12. After 2 days of venoarterial ECMO and 6 days of venovenous ECMO, conventional ventilation was possible. The patient was extubated 1 month after his admission in our unit. Pulmonary arterial hypertension was initially persistent and temporarily treated with sildenafil and bosentan.

The last follow-up at 15 months of age showed no other infection on preventive antibiotic therapy, a growth failure (–4 SD), microcephaly (42 cm, < –2 SD) without any abnormality identified by cerebral CT scan, and a persistent low level of T CD4+ lymphocytes, T CD4+ naive cells, with a normal level of B and NK cells, and a normal IgG count.

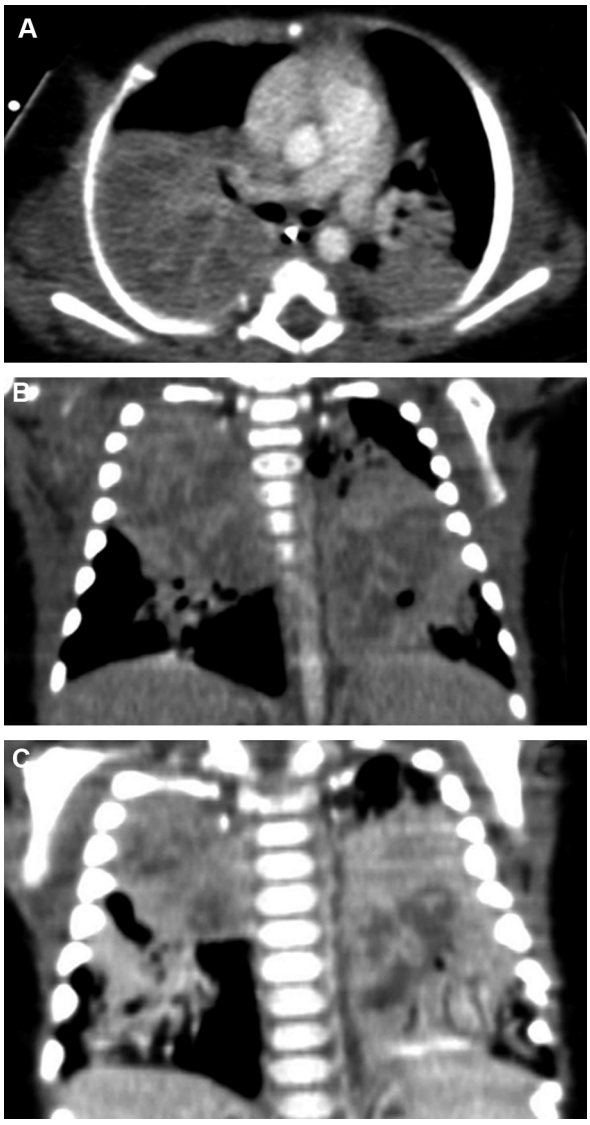

Fig. 1. Chest CT scan, transversal and frontal views with injection. A and B. Two weeks after initial symptoms. Dense infiltrate of the upper right and lower left lobes, with necrotic segments. C. One month later: cavitation aspect and increase in necrotic segments.
Scanner thoracique, coupes transversale et frontale avec injection. A et B. Deux semaines d'évolution. Infiltrat dense du lobe supérieur droit et inférieur gauche avec portion nécrotique. C. Un mois d'évolution : aspect de cavitation et majoration des portions nécrotiques.

3. Discussion

Pediatric LD is probably underestimated and underreported. In the United States, between 1990 and 2005, less than 1% of case patients were younger than 14 years old. The authors of a 2006 pediatric literature review evaluated 76 case patients, of whom 46% were community-acquired [3]. Neonatal case patients accounted for only 13% of all reported pediatric LD cases, but only three case patients were community-acquired [3]. In France, among a total of 11,147 LD case patients reported

Table 1
Results of immunological investigations in a neonate patient presenting with *Legionella pneumophila* infection.
Résultats des explorations immunologiques chez un nouveau-né atteint d'une infection à Legionella pneumophila.

Patient	4 months	Normal values
Lymphocytes	2.6×10^9/L	$3.40–7.20 \times 10^9$/L
T CD3+	0.99×10^9/L	$2.50–5.60 \times 10^9$/L
T CD4+	0.52×10^9/L	$1.80–4.00 \times 10^9$/L
T CD8+	0.34×10^9/L	$0.59–1.60 \times 10^9$/L
T CD4+ CD45RA+ CD31+ (naive)	37%	60–72%
T CD4+ CD45R0+ (memory)	32%	2–22%
T CD8+ CD45RA+ CCR7+ (naive)	82%	52–68%
T CD8+ CD45RA– CCR7+ (central memory)	4%	3–4%
T CD8+ CD45RA– CCR7– (effector memory)	5%	11–22%
T CD8+ CD45RA– CCR7+ (effector memory RA+)	9%	16–28%
B cells (CD19+)	1.14×10^9/L	$0.43–3.00 \times 10^9$/L
NK cells (CD16+CD56+)	0.36×10^9/L	$0.17–0.83 \times 10^9$/L
IgG	6.14 g/L	3–5.5 g/L
IgA	0.07 g/L	0.12–0.38 g/L
IgM	0.46 g/L	0.30–0.85 g/L

Immunological investigations revealed a decreased T CD4+ and CD8+ lymphocyte count, with low percentage of T CD4+ naive cells, and low level of IgA.
Les explorations immunologiques révèlent une diminution du taux de lymphocyte T CD4+ et CD8+, associée à une faible proportion de lymphocytes T CD4+ naïfs et une carence en IgA.

during the 1998–2008 period, only three patients under 3 years of age were diagnosed. None of them was a neonatal case [4,5]. In the extended 1998–2015 period, six patients under 3 years of age (including ours) were reported. The four other case patients were all *Legionella* sg1, with underlying condition such as corticosteroid treatment, cancer, or bone marrow transplantation [unpublished].

Seventy-eight per cent of reviewed pediatric case patients had underlying disease or immunosuppressive condition, such as malignancy, corticosteroid or immunosuppressive treatment, congenital immunodeficiency, and underlying chronic lung or heart disease [3]. However, several cases have been reported in immunocompetent children. In the neonatal population, prematurity should be considered as an immunosuppressive condition and is the main context for neonatal LD. Our case patient had a persistent T CD4+ lymphocytes and T CD4+ naive cells at the age of 15 months. In a context of growth failure and microcephaly, this is consistent with an inborn immunodeficiency, still not characterized. A 2-year follow-up of this patient did not reveal any new severe infection.

Usually described as a rare complication due to *Legionella* species, lung abscesses have been reported in several pediatric cases [5]. In our case, evolution of the initial pneumonia showed two lung necrotic densities with cavitation.

Very few experiences of ECMO are reported in LD. Several successfully treated adult case patients are described, but to our knowledge this is the first case of successful ECMO support in pediatric community-acquired LD.

Legionella urinary antigen tests are not able to detect other serogroups than *L. pneumophila* sg1 explaining a late diagnosis of LD. This infection must be kept in mind in case of severe pneumonia and lung abscesses in children and neonates. In the presence of negative *Legionella* urinary antigen assay, *Legionella* PCR in respiratory samples should be more widely requested for the early detection and treatment of *Legionella* pneumonia in children.

4. Conclusion

LD should be more often detected for severe community-acquired or hospitalized pneumonia in pediatric intensive care units, with or without any immunosuppressive context or underlying condition. The severity of this infection may require the use of ECMO support, which was successful in our case.

Authors' contributions

A.L., J.R. and S.R. wrote the article.
C.P., S.J., A.F. and C.L reviewed the article.

Disclosure of interest

The authors declare that they have no competing interest.

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Letters to the editor

Invasive toxocariasis with hepatic lesions

Toxocarose invasive avec atteinte hépatique

Keywords: Toxocariasis; Visceral larva migrans; Hepatitis

Mots clés : Toxocarose ; Larva migrans viscérale ; Hépatite

1. Introduction

Hypereosinophilia is a common biological finding in travelers coming from tropical areas. Etiological investigation of hypereosinophilia depends on the patient's geographic origin and travel history. The neoplastic and allergic etiologies should also be considered alongside parasitic etiology. The highest rates of hypereosinophilia in parasitic infections are seen with helminth infections. Parasites most frequently associated with massive hypereosinophilia in temperate countries are: *Toxocara canis*, *Fasciola hepatica*, *Ancylostoma* spp., *Strongyloides stercoralis*, *Ascaris lumbricoides, Taenia saginata, Taenia solium*, and *Enterobius vermicularis*.

We report the case of a male patient consulting for hypereosinophilia after traveling to Morocco for three months and complaining about fatigue, myalgia, diarrhea and numbness of the four extremities.

A 52-year-old man without any comorbidity, without any pets at home, and without any specific diet, traveled to India (April–June 2013) and Morocco (December 2013–March 2014). A few days after arrival in the south of France, he presented with a maculopapular rash and itching all over the body excluding hands and feet. Steroid ointment improved the skin lesions. Once the rash resolved, the patient presented with sudden myalgia, and hand and foot paresthesia with deterioration of his health status. The biology results showed: eosinophil count at 5.6 g/L, C-reactive protein < 6 mg/L, normal renal function, aspartate aminotransferase (ASAT) 68 IU/L (normal < 34 IU/L), alanine aminotransferase (ALAT) 34 IU/L (normal < 55 IU/L), gamma-glutamyl transpeptidase (γGT) 45 IU/L (normal: 12–64 IU/L), creatine phosphokinase (CPK) 782 IU/L (normal: 30–200 IU/L), total bilirubin 8 mg/L (normal < 12 mg/L). The results of the hepatic ultrasound showed a normal liver size with several oval hypoechoic elements of a few centimeters, also seen at the CT-scan. In May 2014, the physical examination revealed extreme fatigue, numbness of both hands and feet, and hyporeflexia of the lower limbs. Three parasitic stool examinations were performed and fascioliasis, trichinellosis, cysticercosis, strongyloidiasis and amoebiasis serologies were negative. Eosinophilia was still high at 3.6 g/L. The electromyography of the four limbs showed no abnormality except for a left hand carpal tunnel syndrome. Serology for *T. canis* was strongly positive (ELISA test 77.6 IU/L, and Western Blot positive 5 stripes). Hepatic lesions were not biopsied as they were not collected. The diagnosis of visceral larva migrans (VLM) was established. Treatment with albendazole (100 mg/kg for 15 days) was initiated and the patient's *clinical condition improved.* He started working again and the numbness of the four limbs disappeared quickly. At the end of treatment, eosinophilia was at 2.7 g/L. The results of the hepatic ultrasound showed hypoechoic lesions of a few millimeters. All symptoms had entirely disappeared a few weeks later.

T. canis is one of the most important zoonosis also observed in dogs, cats and some wild host (e.g. foxes). *T. canis* is more prevalent in tropical areas, in developing countries where dog treatment and population control is limited, in Eastern Europe where the seroprevalence for *Toxocara*-specific antibodies ranges from 10% to 32% [1,2]. Humans are infected by ingesting embryonated eggs shed by definitive hosts, or by consuming raw or undercooked paratenic host containing embryonated eggs. Following a first infection, pets and litters should be treated to avoid subsequent infection. Physiological reactions to *Toxocara* infection are related to the host's immune response and the parasitic load. Most cases of *Toxocara* infection are asymptomatic, especially in adults. The clinical symptoms are caused by the migration of *Toxocara* larvae via the bloodstream to internal organs such as muscles, liver, brain and eyes [1]. Few clinical presentations involving liver injury have been reported in the literature; liver involvement in larva migrans infection can be wrongly interpreted as a tumor [3] or a pyogenic abscess. Rayes et al. performed a small case control study and suggested that human toxocariasis could be one of the predisposing causes of pyogenic liver abscess [4]. Hepatic lesion with eosinophilia can also be caused by *Ascaris* and *Ancylostoma* species. Visceral larva migrans liver nodules are usually subtle, poorly discernable, and ill-defined margins can be observed at ultrasound. This helps in differentiating them from metastatic deposits for instance. Visceral larva migrans liver nodules may also have definite cystic component, which makes diagnosis more difficult [5]. Our patient presented with no other liver abnormality; HIV, HBV, and HCV serology was

negative; and he did not have any alcohol abuse. No relapse was observed during the eight-month follow-up and only one treatment with albendazole was initiated. An early diagnosis and treatment prevented this patient from having to undergo liver biopsy or surgery. Although liver presentations of toxocariasis are quite frequent in ubiquitous diseases, it is frequently forgotten in the clinical decisional management of adults.

Contributors

Y.K. and L.L. wrote the article. Y.K. and C.L. took care of the patient management when hospitalized. A.S. reviewed the article.

Disclosure of interest

The authors declare that they have no competing interest.

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Spondylodiscite lombaire à *Neisseria meningitidis* W135

Primary lumbar spondylitis due to Neisseria meningitidis W135

Mots clés : Spondylodiscite lombaire ; Infections à méningocoques ; *Neisseria meningitidis*

Keywords: Lumbar spondylitis; Meningococcal infections; *Neisseria meningitidis*

1. Introduction

Les tableaux cliniques d'infection à méningocoques sont variés, allant du simple portage asymptomatique aux présentations classiques de choc septique ou de méningite. Les arthrites primitives à *Neisseria meningitidis* sont rares mais classiquement décrites dans la littérature. Selon les séries, elles surviennent principalement avec un tableau de méningite associée [1] ou au contraire plutôt sans signe de septicémie ni syndrome méningé [2]. On constate en France, depuis 2000, un nombre croissant d'infections à *Neisseria meningitidis* de sérogroupe W135 depuis la description du premier cas enregistré en 1994 [2]. Les premières observations de spondylodiscites à *Neisseria meningitidis* ont été rapportées lors de procédures invasives ou lors de situations d'errance diagnostique après une méningite non traitée [3]. En 2000, Apfalter et al. ont décrit un cas d'arthrite primitive de hanche chez un garçon de 13 ans immunocompétent [4]. Dans cette observation, *Neisseria meningitidis* du sérogroupe W135 a été isolé dans la culture du liquide synovial de hanche. En 2006, Mendes et al. ont rapporté un premier cas de spondylodiscite cervicale à *Neisseria meningitidis* du groupe B chez un homme de 47 ans [5].

2. Cas clinique

Un homme de 54 ans, non éthylo-tabagique, fut admis dans le service de médecine interne début octobre 2013 pour une lombalgie intense d'horaire mixte avec possibles frissons associés. Il avait bénéficié de soins dentaires en 2010 et avait subi un traumatisme lombaire dans un accident de la voie publique en janvier 2013 compliqué d'un tassement du plateau supérieur de L1. Il avait voyagé 2 mois auparavant en Chine, au Liban et au Mexique pour raisons professionnelles. Il eut, 10 jours avant son hospitalisation, un contact rapproché avec sa sœur de retour d'un séjour de 2 semaines en Côte d'Ivoire en septembre 2013. Il n'avait subi aucune procédure invasive diagnostique ou thérapeutique dans l'année. Il développait, 4 jours avant l'admission, un tableau de lumbago hyperalgique pseudofracturaire, d'horaire mixte, associée à une asthénie et des nausées. Il présentait une impotence majeure nécessitant la mise sous opiacés après échec des anti-inflammatoires non stéroïdiens (kétoprofène) reçus pendant 3 jours. À l'examen physique, le patient était apyrétique, sans éruption cutanée. On ne notait aucune blessure ni lésion pharyngée. L'examen

negative; and he did not have any alcohol abuse. No relapse was observed during the eight-month follow-up and only one treatment with albendazole was initiated. An early diagnosis and treatment prevented this patient from having to undergo liver biopsy or surgery. Although liver presentations of toxocariasis are quite frequent in ubiquitous diseases, it is frequently forgotten in the clinical decisional management of adults.

Contributors

Y.K. and L.L. wrote the article. Y.K. and C.L. took care of the patient management when hospitalized. A.S. reviewed the article.

Disclosure of interest

The authors declare that they have no competing interest.

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Spondylodiscite lombaire à *Neisseria meningitidis* W135

Primary lumbar spondylitis due to Neisseria meningitidis W135

Mots clés : Spondylodiscite lombaire ; Infections à méningocoques ; *Neisseria meningitidis*

Keywords: Lumbar spondylitis; Meningococcal infections; *Neisseria meningitidis*

1. Introduction

Les tableaux cliniques d'infection à méningocoques sont variés, allant du simple portage asymptomatique aux présentations classiques de choc septique ou de méningite. Les arthrites primitives à *Neisseria meningitidis* sont rares mais classiquement décrites dans la littérature. Selon les séries, elles surviennent principalement avec un tableau de méningite associée [1] ou au contraire plutôt sans signe de septicémie ni syndrome méningé [2]. On constate en France, depuis 2000, un nombre croissant d'infections à *Neisseria meningitidis* de sérogroupe W135 depuis la description du premier cas enregistré en 1994 [2]. Les premières observations de spondylodiscites à *Neisseria meningitidis* ont été rapportées lors de procédures invasives ou lors de situations d'errance diagnostique après une méningite non traitée [3]. En 2000, Apfalter et al. ont décrit un cas d'arthrite primitive de hanche chez un garçon de 13 ans immunocompétent [4]. Dans cette observation, *Neisseria meningitidis* du sérogroupe W135 a été isolé dans la culture du liquide synovial de hanche. En 2006, Mendes et al. ont rapporté un premier cas de spondylodiscite cervicale à *Neisseria meningitidis* du groupe B chez un homme de 47 ans [5].

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neurologique était normal, sans aucun signe méningé. Les examens biologiques révélaient une leucocytose à $11{,}75 \times 10^9$/L à polynucléaires neutrophiles ($10{,}34 \times 10^9$/L), une vitesse de sédimentation à 45 mm à la 1re heure, et une protéine C réactive très élevée à 366 mg/L. Le taux de créatinine initial était de 302 μmol/L et se normalisa rapidement après hydratation et arrêt du kétoprofène. L'échographie rénale était normale. L'uricémie était élevée à 940 μmol/L et la calcémie initiale à 2,64 mmol/L. Des signes d'arthropathie dégénérative aspécifique de L2–L3 étaient constatés en scanner du rachis lombaire. Étant donné le tableau hyperalgique, la polynucléose, le taux de protéine C réactive, une spondylodiscite infectieuse fut suspectée, une imagerie par résonance magnétique fut pratiquée et des hémocultures furent ensemencées. Après injection de gadolinium, l'imagerie par résonance magnétique montrait des hypersignaux T2 des plateaux vertébraux de L2 et L3, du disque L2–L3, des muscles paravertébraux, et une prise de contraste sur l'articulaire postérieure de L5 droite. Il n'y avait pas d'abcès épidural. Quatre hémocultures révélèrent la présence de diplocoques à gram négatif. *Neisseria meningitidis* du sérogroupe W135 fut identifié par l'Institut Pasteur de Paris. La concentration minimale inhibitrice de benzylpénicilline était de 0,380 mg/L. Le patient reçut initialement 8 g/jour d'amoxicilline et 240 mg/jour de gentamycine. Devant la sensibilité diminuée à la pénicilline (concentration minimale inhibitrice de 0,750 mg/L), le traitement fut modifié à la faveur de 2000 mg/jour de ceftriaxone associée à 240 mg/j de gentamycine pendant 4 semaines par voie veineuse (concentration minimale inhibitrice de la souche pour le cefotaxime de 0,012 mg/L). Le patient reçut ensuite une association de ciprofloxacine 1500 mg associé à 1600 mg/jour de rifampicine pendant 8 semaines supplémentaires en service de rééducation (concentrations minimales inhibitrices respectives de 0,004 et 0,023 mg/L pour cette souche). Le patient présenta une éruption maculopapuleuse sur les membres inférieurs pendant 3 jours, n'évoquant pas des lésions purpuriques de *Neisseria meningitidis* et disparaissant spontanément sans traitement. L'électrophorèse des protéines plasmatiques était normale, et les sérologies VIH 1 et 2 négatives. On ne retrouvait aucun signe en faveur d'une endocardite en échocardiographie. Un corset lombaire et un repos en décubitus strict pendant 4 semaines furent nécessaires avant de suspendre définitivement les morphiniques. La protéine C réactive était respectivement à 28 puis 7 mg/L, après 2 puis 5 semaines d'antibiothérapie. Plusieurs hémocultures prélevées 7 jours après le début du traitement antibiotique demeurèrent stériles. En décembre 2013, le scanner du rachis lombaire montrait des condensations et des érosions des plateaux vertébraux de L2–L3 compatibles avec des séquelles de spondylodiscite infectieuse. Au prix d'une raideur résiduelle, la guérison fut obtenue.

3. Discussion

À notre connaissance, il s'agit du premier cas de spondylodiscite lombaire à *Neisseria meningitidis* de sérogroupe W135. Il n'existait aucun signe de méningite et le portage pharyngé ne fut pas testé. Une association significative a été établie par Vienne et al. entre les souches du sérogroupe W135, appartenant majoritairement à un groupe clonal ET-37, et les arthrites septiques à *Neisseria meningitidis* [2]. Dans notre observation, nous ne savons pas si la souche isolée appartenait au même groupe clonal. Dans le cas de spondylodiscite cervicale à *Neisseria meningitidis* du groupe B rapporté par Mendes et al. [5], il existait un passé d'abcès pharyngé 2 mois avant l'épisode. Les hémocultures étaient demeurées stériles et le diagnostic bactériologique avait été établi sur les cultures de biopsies de disque intervertébral. Le patient présentait un abcès épidural associé à la spondylodiscite et le traitement avait comporté une discectomie en association avec l'antibiothérapie. Dans notre cas, le contact rapproché récent avec sa sœur revenue d'Afrique de l'Ouest explique probablement l'origine de la souche avant une diffusion hématogène. Cependant, nous n'avons pu identifier avec certitude le sujet contact. Nous avons choisi un traitement initial par céphalosporines de 3e génération à la posologie de 2000 mg/j en association aux aminosides, d'une part en raison de la sensibilité diminuée de la souche à la pénicilline, et d'autre part pour s'assurer d'une concentration osseuse suffisante de la ceftriaxone à la dose de 2000 mg/j. En l'absence de recommandation sur les spondylodiscites à méningocoque, nous avons décidé de prolonger le traitement par deux molécules à bonne pénétration osseuse (rifampicine et ciprofloxacine) pour une durée totale de 12 semaines. En l'absence d'abcès épidural et devant la bonne évolution sous antibiotiques, nous avons décidé de ne pas procéder à un geste chirurgical complémentaire.

Par ailleurs, la goutte tophacée peut être responsable de tableaux cliniques similaires. Barrett et al. rapportent une série de 37 cas de goutte de localisation vertébrale mimant une infection épidurale [6]. Notre patient ne présentait ni antécédent d'accès goutteux, ni anomalie de l'examen articulaire périphérique à son admission ou pendant son séjour. L'uricémie s'est immédiatement normalisée après réhydratation et correction de l'insuffisance rénale aiguë. L'imagerie par résonance magnétique au diagnostic montrait un hypersignal T2 des plateaux vertébraux et des muscles paravertébraux qui peuvent être rencontrés dans les spondylodiscites infectieuses ou microcristallines. Les anomalies scanographiques après 2 mois de traitement peuvent se voir dans les deux pathologies également. Les radiographies des 2 mains, des genoux et des pieds ne révélaient aucun signe de goutte tophacée. Il n'y avait pas non plus d'argument biologique ou radiologique pour une chondrocalcinose.

4. Conclusion

Le pronostic des arthrites à *Neisseria meningitidis* est excellent après traitement. Il semble qu'une antibiothérapie à bonne diffusion osseuse bien conduite, telle que ciprofloxacine et rifampicine, permette une guérison des spondylodiscites à *Neisseria meningitidis* des sérogroupes B et W135, qu'il y ait drainage chirurgical ou non.

Comme le rapportaient Vienne et al., un nombre croissant d'arthrites à *Neisseria meningitidis* de sérogroupe W135 est constaté depuis 2000 [2]. Trois des quatre cas étaient décrits chez des pèlerins de retour du Hadj en 2000. Il nous semble qu'un séjour

récent en Afrique ou un contact rapproché avec un voyageur de retour de ce continent, doit être systématiquement recherché chez un sujet présentant une infection ostéoarticulaire à *Neisseria meningitidis* W135. Cependant, une localisation vertébrale de la goutte tophacée ou de la chondrocalcinose peut également être évoquée chez les adultes d'âge moyen présentant une spondylodiscite sans fièvre avant d'envisager une biopsie du disque intervertébral en l'absence d'abcès épidural.

Contributions des auteurs

C. de Villelongue a écrit l'article.

F. Tilly était le médecin traitant du patient et a corrigé l'article.

B. Dell'Isola est à l'origine du rapport de l'étude cas et a corrigé l'article.

Déclaration de liens d'intérêts

Les auteurs n'ont pas précisé leurs éventuels liens d'intérêts.

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Abcès pulmonaire à *Gallibacterium anatis*

Gallibacterium anatis pulmonary abscess

Mots clés : Abcès ; *Gallibacterium anatis*

Keywords: Abscess; *Gallibacterium anatis*

Gallibacterium anatis est une bactérie Gram négatif de la famille des Pasteurellaceae. Elle est connue par les vétérinaires comme une bactérie commensale des muqueuses des voies respiratoires supérieures et du tractus génital des poulets sains [1]. Elle peut cependant être responsable d'authentiques infections respiratoires, de péritonites et de salpingites chez le poulet [2,3]. Elle n'a été décrite en pathologie humaine que deux fois, la première sous la forme d'une bactériémie chez un patient immunodéprimé [4] et la deuxième fois elle a été isolée à partir d'un examen cytobactériologique des crachats (ECBC) chez un patient atteint de bronchite chronique [5]. Nous rapportons ici le premier cas chez l'homme d'abcès pulmonaire à *G. anatis*.

Un homme de 71 ans a été hospitalisé en septembre 2013 pour exploration d'une altération de l'état général avec une perte de 7 kg en 4 mois. Il présentait également une douleur latéro-thoracique gauche aggravée à la toux et plus récemment un syndrome subocclusif.

Dans ses antécédents médicaux, on notait un tabagisme sevré, une hypertension artérielle, une hypercholestérolémie, un pontage aorto-bifémoral et une cardiopathie ischémique.

À l'arrivée dans le service, il était fébrile à 38,7 °C, normotendu et eupnéique en air ambiant.

L'auscultation cardio-pulmonaire était normale. La palpation abdominale retrouvait une masse périombilicale sensible sans défense.

La biologie retrouvait un CRP à 70 mg/L, des polynucléaires neutrophiles à 14,7 g/L et une albumine à 14 g/L.

Le scanner thoraco-abdomino-pelvien mettait en évidence une masse excavée de 4 × 3 cm à parois épaisses avec niveau hydro-aérique du lobe supérieur gauche ainsi qu'une invagination jéjuno-jéjunale sur probable lésion tumorale sous-jacente.

Une hémoculture périphérique revenait positive à *Escherichia coli* résistant à l'amoxicilline, à l'amoxicilline–acide clavulanique, à la ticarcilline, intermédiaire à la pipéracilline– tazobactam, sensible à la ceftriaxone, à la gentamicine, à l'ofloxacine et au cotrimoxazole. À l'examen direct du liquide de lavage broncho-alvéolaire (LBA), on retrouvait de très nombreux polynucléaires avec de nombreux cocci à Gram positif et bacilles à Gram positif. En culture, 10^4 unités formant colonie/mL (UFC/mL) *E. coli* et 10^4 UFC/mL *G. anatis* étaient identifiés par spectrométrie de masse de type *matrix-assisted*

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laser desorption ionization–time of flight (MALDI-TOF) sur l'automate Microflex (Bruker Daltonics).

L'isolat de *G. anatis* était sensible à l'amoxicilline, à la ceftriaxone, à l'ofloxacine, à l'amikacine, à la colistine et résistant au cotrimoxazole.

Une antibiothérapie parentérale associant la ceftriaxone à 2 grammes/jour et l'amikacine 750 mg/jour était administrée pendant dix jours, puis la ceftriaxone était poursuivie seule pour une durée totale de 5 semaines.

Devant la dénutrition sévère, une nutrition parentérale était entreprise.

L'évolution était favorable sur le plan infectieux avec une régression de la fièvre et du syndrome inflammatoire biologique.

Le contrôle scannographique à 3 mois retrouvait à la place de l'abcès intra-parenchymateux pulmonaire une lésion séquellaire sous-pleurale rétractile de 2 × 1,5 cm avec dilatation par traction des bronches périphériques. Il n'y avait pas d'argument pour une néoplasie pulmonaire sous-jacente.

Fin mai 2014, le patient bénéficiait d'une résection grêlique segmentaire pour son invagination intestinale. L'histologie de la pièce opératoire mettait en évidence un adénome tubulo-villeux en néoplasie intra-épithéliale de haut grade.

En août 2014, il avait repris sept kilogrammes et n'avait plus aucun signe fonctionnel digestif ni pulmonaire.

G. anatis est une bactérie le plus souvent rencontrée en milieu vétérinaire. Elle a été isolée chez de nombreux oiseaux, poulets, canards, oies mais aussi chez la dinde et le cochon [6]. Elle appartient à la famille des *Pasteurellaceae.* Initialement affiliée au genre *Pasteurella* (*P. anatis*), cette espèce a été transférée dans un nouveau genre bactérien *Gallibacterium* en 2003. Six espèces de *Gallibacterium* sont actuellement identifiées. Cette espèce ne présente pas de caractère particulier de culture et est capable de se développer sur les milieux de culture bactérienne utilisés en routine diagnostique comme la gélose au sang. Les méthodes d'identification basée sur la spectrométrie de masse MALDI-TOF sont à même d'identifier cette espèce. À la différence du cas présenté par Aubin et al., il n'y a pas eu besoin d'avoir recours à l'identification moléculaire par PCR-séquençage du gène de l'ARNr 16S. La base de données utilisée par le MALDI biotyper (Bruker Daltonics) référence actuellement près de 6000 espèces dont *G. anatis* offrant un moyen rapide, peu onéreux et fiable d'identification des bactéries peu rencontrées en bactériologie médicale.

G. anatis est en effet habituellement absente de la flore bactérienne commensale chez l'homme.

Le 1er cas rapporté de bactériémie à *G. anatis* a été décrit chez un patient immunodéprimé atteint de mucoviscidose et ayant bénéficié d'une greffe bipulmonaire. Notre patient était lui aussi immunodéprimé par une dénutrition sévère.

Il s'agit donc probablement d'une bactérie très peu virulente chez l'homme mais qui, dans des conditions d'immunodépression sévère, peut devenir un pathogène opportuniste. Ainsi, plusieurs facteurs de virulence ont été identifiés chez *G. anatis*, parmi lesquels la RTX (*repeat in toxin*) toxine GtxA, la capsule polysaccharidique, la sécrétion de métalloprotéases capable de dégrader les immunoglobulines IgG aviaires et la capacité de certaines souches d'agglutiner les hématies aviaires.

Notre patient présentait une atteinte pulmonaire sous la forme d'un abcès. Les abcès pulmonaires sont typiquement rencontrés chez les patients immunodéprimés, que ce soit par un diabète, par une corticothérapie au long cours ou par une dénutrition sévère.

Les bactéries les plus souvent en cause dans les abcès pulmonaires sont originaires des voies aériennes supérieures et bucco-dentaires. Chez notre patient qui n'était pas en contact avec des gallinacés, on peut se poser la question d'une contamination alimentaire par de la volaille, voire éventuellement des œufs. En effet la présence simultanée d'*E. coli* sur les hémocultures et sur le liquide de LBA est en faveur d'un mécanisme de translocation digestive *d'E. coli* et de *G. anatis* chez ce patient opéré quelques mois plus tard d'une invagination intestinale secondaire à un adénome tubulo-villeux grêlique.

L'évolution de l'infection a été favorable sous antibiothérapie parentérale prolongée, sans nécessité de recours à la chirurgie thoracique. En effet, au cours des abcès pulmonaires, le traitement antibiotique seul permet la guérison dans 80 à 90 % des cas [7].

Contribution des auteurs

C. de Moreuil, G. Héry-Arnaud, M.S. Fangous et R. Le Berre ont toutes les quatre participé à la rédaction de cet article et à sa relecture pour corrections.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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